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9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analysis if the data were available.

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* *From* Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1-3, 1985)

Contents

Cancer Treatment Reports
Volume 69, Number 11
November 1985

Editorial

1235 The Phase II Trial. **R. E. Wittes, S. Marsoni, R. Simon, and B. Leyland-Jones.** National Cancer Institute, Bethesda, Maryland

Clinical Studies

1241 Cyclic Alternating Chemotherapy for Small Cell Carcinoma of the Lung. **N. Murray, A. Shah, K. Wilson, J. Goldie, N. Voss, C. Fryer, P. Klimo, P. Coy, E. Hadzic, G. Gudauskas, and R. Fowler.** Cancer Control Agency of British Columbia, and University of British Columbia, Vancouver, Canada

1243 Comparison of Cyclophosphamide Plus Cisplatin Versus Hexamethylmelamine, Cyclophosphamide, Doxorubicin, and Cisplatin in Combination as Initial Chemotherapy for Stage III and IV Ovarian Carcinomas. **J. H. Edmonson, G. W. McCormack, T. R. Fleming, S. A. Cullinan, J. E. Krook, G. D. Malkasian, K. C. Podratz, J. A. Mailliard, J. A. Jefferies, J. F. Barlow, and H. E. Windschitl.** North Central Cancer Treatment Group and Mayo Clinic, Rochester, Minnesota

1249 Tastes Associated With Parenteral Chemotherapy for Breast Cancer. **J. H. Fetting, P. M. Wilcox, V. R. Sheidler, J. P. Enterline, R. C. Donehower, and L. B. Grochow.** The Johns Hopkins University School of Medicine, Baltimore, Maryland

1253 Cisplatin Bolus and 5-FU Infusion Chemotherapy for Non-Small Cell Lung Cancer. **P. L. Weiden, A. B. Einstein, and R. H. Rudolph.** Virginia Mason Medical Center, Seattle, Washington

1257 Consecutive Dose-Finding Trials Adding Lorazepam to the Combination of Metoclopramide Plus Dexamethasone: Improved Subjective Effectiveness Over the Combination of Diphenhydramine Plus Metoclopramide Plus Dexamethasone. **M. G. Kris, R. J. Gralla, R. A. Clark, L. B. Tyson, J. J. Fiore, D. P. Kelsen, and S. Groshen.** Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, New York

1263 Tolerance to Antineoplastic Agents in Children and Adults. **S. Marsoni, R. S. Ungerleider, S. B. Hurson, R. M. Simon, and L. D. Hammershaimb.** National Cancer Institute, Bethesda, Maryland

Phase I–II Trials

1271 Phase II Study of Low-Dose Mitomycin in Patients With Ovarian Cancer Previously Treated With Chemotherapy. **R. H. Creech, M. K. Shah, R. B. Catalano, K. Dierks, H. Dayal, and R. Goldberg-Alberts.** American Oncologic Hospital, The Fox Chase Cancer Center, Philadelphia, Pennsylvania

1275 Phase II Trial of Epirubicin in Gastric Cancer. **J. H. Scarffe, J. B. Kenny, R. J. Johnson, S. E. Owens, G. R. Giles, S. H. Leveson, and W. V. Maley.** Christie Hospital and Holt Radium Institute, Manchester, England

Clinical and Preclinical Pharmacology

1279 Pharmacokinetic Evaluation of Increasing Dosages of Etoposide in a Chronic Hemodialysis Patient. **J. J. M. Holthuis, F. L. Van de Vyver, W. J. van Oort, H. Verleun, A. B. Bekaert, and M. E. De Broe.** State University Utrecht, The Netherlands

1283 Enhancement of Tumorigenicity of B16 Melanoma in Heterogenetic Mice by Administration of Copper Chelates. **H. F. Pierson.** National Cancer Institute, Bethesda, Maryland

1293 Potentiation and Protection of Doxorubicin Cytotoxicity by Cellular Glutathione Modulation. **A. Russo and J. B. Mitchell.** National Cancer Institute, Bethesda, Maryland

BRIEF REPORTS

1297 Treatment of Chronic Myelogenous Leukemia in Blastic Crisis With Chemotherapy Incorporating Vindesine-Prednisolone. **Y. Uzuka and Y. Saito.** Tohoku University, Sendai, Japan

1301 Comparison of the Antiemetic Efficacy of Two High-Dose Benzamides, Metoclopramide and Alizapride, Against Cisplatin-Induced Emesis. **R. Saller and D. Hellenbrecht.** University Clinics of Frankfurt am Main, Federal Republic of Germany

1305 Carboplatin: A New Platinum Analog in the Treatment of Epidermoid Carcinoma of the Esophagus. **C. Sternberg, D. Kelsen, M. Dukeman, L. Leichman, and R. Heelan.** Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, New York

1309 Metoclopramide in Vincristine-Induced Ileus. **H. S. Garewal and W. S. Dalton.** University of Arizona, Arizona Health Sciences Center, Tucson

1313 Phase II Trial of 5-FU, Vincristine, and Mitomycin (FOMi) in Metastatic Bronchioloalveolar Cell Lung Cancer: A Southwest Oncology Group Study. **T. P. Miller and R. B. Livingston.** Southwest Oncology Group

1315 Phase II Study of Aclarubicin in Patients With Lymphoma. **D. C. Case, Jr, M. A. Boyd, and D. M. Hayes.** Maine Medical Center, Portland

1317 Continuous-Infusion Vindesine in Refractory Carcinoma of the Cervix: A Phase II Trial. **J. J. Kavanagh, P. B. Saul, D. M. Gershenson, L. J. Copeland, and J. T. Wharton.** The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

1319 Phase II Trial of 4′-Deoxydoxorubicin in Patients With Advanced Breast Cancer. **S. P. Leitner, E. S. Casper, T. B. Hakes, R. J. Kaufman, R. J. Winn, M. Scoppetuolo, V. Raymond, N. L. Geller, and C. W. Young.** Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, New York

1321 Phase II Trial of Mitoxantrone in Multiple Myeloma: A Southwest Oncology Group Study. **D. S. Alberts, S. P. Balcerzak, J. D. Bonnet, and R. L. Stephens.** Southwest Oncology Group

1325 Drug Precipitation Within Iv Tubing: A Potential Hazard of Chemotherapy Administration. **M. H. Cohen, A. Johnston-Early, M. A. Hood, M. McKenzie, M. L. Citron, N. Jaffe, and S. H. Krasnow.** Washington Veterans Administration Medical Center, Washington, DC

CLINICAL TRIALS SUMMARIES

1327 Aclarubicin Given as Continuous Infusion in Non-Small Cell Bronchogenic Carcinoma. **D. F. Chiuten, T. Umsawasdi, H. M. Dhingra, G. P. Bodey, and M. Valdivieso.** The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston

1329 Mitoxantrone in Adenocarcinoma of the Endometrium: A Southwest Oncology Group Study. **R. D. Hilgers, D. D. Von Hoff, R. L. Stephens, J. G. Boutselis, and S. E. Rivkin.** Southwest Oncology Group

1331 Phase II Trial of Dianhydrogalactitol in the Treatment of Children With Refractory Childhood Malignancies: A Report From the Childrens Cancer Study Group. **J. Z. Finklestein, N. Shore, W. Krivit, D. Hammond, and G. Higgins.** Childrens Cancer Study Group

1335 Phase II Trial of Etoposide, Vincristine, and High-Dose Cisplatin in Advanced Non-Small Cell Lung Cancer. **M. Bertrand, P. Multhauf, C. Presant, D. Rappaport, D. W. Blayney, B. I. Carr, G. Cecchi, J. H. Doroshow, E. Emont, D. Goldberg, N. Kogut, L. Leong, and K. Margolin.** City of Hope National Medical Center, Duarte, California

1337 Phase II Trial of 4′-Deoxydoxorubicin in Advanced Non-Small Cell Lung Cancer. **S. Kaplan, C. Sessa, R. Joss, J. P. Obrecht, P. Siegenthaler, and F. Cavalli.** Swiss Group for Clinical Cancer Research

LETTERS

1339 Clinical Predictivity of Transplantable Tumor Systems in the Selection of New Drugs for Solid Tumors: Reply to a Commentary. **M. J. Staquet, D. P. Byar, S. B. Green, and M. Rozencweig.** European Organization for Research on Treatment of Cancer, Brussels, Belgium

1340 Hypoglycemia: Not an Important Side Effect of Mitoguazone. **B. J. Foster, K. Clagett-Carr, P. J. O'Dwyer, and B. Leyland-Jones.** National Cancer Institute, Bethesda, Maryland

1341 Advanced Ovarian Carcinoma: Response to the Agonist D-Trp-6-LHRH. **H. Parmar, J. Nicoll, A. Stockdale, A. Cassoni, R. H. Phillips, S. L. Lightman, and A. V. Schally.** Westminster Hospital and Medical School, London, United Kingdom

1342 Liver Enzyme Abnormalities After Poly ICLC Infusions. **W. A. Hess, C. T. Bever, and D. E. McFarlin.** Clinical Center, National Institutes of Health, Bethesda, Maryland

1342 Skeletal Muscle Biopsies in Patients Treated With Doxorubicin. **H. Havsteen, I. Brynjolf, B. Hainau, and P. Dombernowsky.** Copenhagen University Hospital, Denmark

1345 ANNOUNCEMENTS

EDITORIAL

The Phase II Trial[1]

Robert E. Wittes,* Silvia Marsoni, Richard Simon, and Brian Leyland-Jones[2,3]

Each phase of clinical drug development presents its own set of dilemmas. Although the goal of phase II is conceptually straightforward, a number of practical and theoretical problems combine to make it perhaps the most treacherous step in clinical drug testing.

The specific purpose of phase II is to develop estimates of the response rate of patients with specified tumor types to a particular drug. To do this, one treats a population of patients with a dose previously determined to be tolerable in phase I. The patients treated in phase II must have tumor that can somehow be objectively assessed. After a defined period of time on treatment, extent of tumor is reassessed, compared with the patient's baseline extent of disease, and the effect of the drug categorized. Generally, treatment continues until either the cancer progresses or the patient develops unacceptable side effects. The chief endpoints of interest are the response rates in the various cancers tested, the durations of response, and the toxic cost of achieving therapeutic effects. Although phase II trials are usually not comparative in design, investigators consider their results in light of all available knowledge about the treatment of a cancer to decide whether further trials are justified.

Phase II, therefore, is intended to determine activity. It does not determine efficacy; the question of whether a new treatment is a useful addition to the therapeutic armamentarium is explicitly a comparative one and cannot be addressed without a carefully selected control population. Since, however, phase II results do determine whether a new treatment should be pursued further, the outcome of phase II is clearly a decisive point in a drug's development.

Since the discovery of new active agents is an obvious priority in the search for better cancer treatment, it would seem logical to utilize a testing strategy that permits the identification of drug activity as expeditiously as possible, while simultaneously limiting the chance of getting false-negative results. Let us now examine the most important variables in phase II to see how these goals might be accomplished most effectively.

Selection of Drugs

In theory, any agent for which tolerable and reproducible biological effects can be defined in phase I should go into phase II testing. As has been previously pointed out, however, many agents do not receive a full phase II evaluation (1). Unmanageable toxic effects (2,3), side effects that are not clearly dose-dependent (4), and disenchantment with an agent that fails to show anticancer activity in phase I (5) have all resulted in truncated phase II evaluations. Agents whose dose-limiting toxic effects are other than bone marrow suppression are particularly likely to be evaluated incompletely (1).

Elsewhere, we have discussed the problems posed by dose-limiting toxic effects other than myelosuppression (1). The intense current interest in exploring the activity of very high doses of many agents, with the infusion of autologous or allogeneic bone marrow to obviate the effect of marrow toxicity, shows that clinical investigators are clearly willing to face the problems of nonmarrow toxic effects if they believe that antitumor effects are likely concomitants of drug administration. Moreover, several agents do in fact possess useful clinical activity at doses not producing significant bone marrow suppression (vincristine, bleomycin, streptozocin, and cisplatin). The lesson is clearly that dose-limiting toxicity other than bone marrow is not in itself reason to curtail progression of a drug into phase II.

Several agents with dose-limiting toxic effects other than bone marrow are currently in clinical development. Some of these, such as tiazofurin and PALA, are highly selective enzyme inhibitors. The definition of the role of such agents in the therapeutic armamentarium, whether as direct cytotoxic agents or as biochemical modulators, remains to be determined. Other agents of current interest with nonmyelosuppressive dose-limiting toxic effects, such as *N*-methylformamide and spiromustine, have led investigators to search for ways of ameliorating hepatic and CNS toxic effects, respectively. Where this can be done, a fuller exploration of the dose-response curve of

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TABLE 1.—Spectrum of clinical activity for 22 evaluable drugs tested since 1975

	No. of drugs evaluated
Leukemia	12
Lymphoma	10
Breast cancer	15
Colon cancer	18
Lung cancer	15
Melanoma	11
Head and neck cancer	11
Renal cancer	11
Sarcoma	10
Ovarian cancer	9
Pancreatic cancer	5
Stomach cancer	4
Myeloma	5
Central nervous system cancer	3
Cervical cancer	3
Prostatic cancer	3
Bladder cancer	5

the agent becomes possible.

On the face of it, the absence of responses in a phase I study should also not impede phase II evaluation. This is so for several familiar reasons relating to criteria for patient selection in phase I trials and to the fact that many patients in a phase I study are treated with doses that are presumably well below a potentially therapeutic dose. Nevertheless, if it is logical to ask whether activity in preclinical murine models can predict clinical activity, it is no less reasonable to ask the same question of therapeutic results in phase I. A detailed characterization of responses in phase I trials is currently in progress (6). On the basis of available preliminary information, however, it appears unlikely that a meaningful answer to this question can be derived retrospectively, because neither the published literature nor the information on file at the National Cancer Institute (NCI) contains enough data with respect to evaluability for response and assessment of the responses themselves.

At present, therefore, except for limiting toxic effects which are not clearly dose-dependent and/or are very severe, there are no good medical or scientific grounds for terminating a drug's clinical development short of a phase II evaluation.

Selection of Diseases

Once a drug enters phase II it is evaluated in a variety of tumor types. Since 1975, 44 drugs have been brought to clinical evaluation under NCI sponsorship. Twenty-two drugs are evaluable for activity at this time. Table 1 shows the spectrum of diseases in which these 22 drugs were evaluated. Not surprisingly, cancers which are common or are known to be sensitive to chemotherapy tend to be the most completely explored. Several important questions may be asked about the optimal strategy for the selection of diseases for phase II testing.

(*a*) Are there any preclinical models which may serve as reliable predictors of response (or nonresponse) for the various cancers? We are currently analyzing the relationship between activity in transplantable and xenograft models and in the clinic. A recently published analysis limited to four human solid tumors suggested little correlation (7). An NCI-supported study of the use of the human tumor colony-forming assay (HTCFA) as a screening tool for selection of agents for clinical trial (8) is of particular interest, since drugs which are negative in the conventional in vivo murine screens will for the first time undergo clinical testing. In principle, the HTCFA or other in vitro approaches based on human tumors might be useful in developing disease-specific information about in vitro drug activity for correlation with results of clinical trials. Clearly, the technology of growing human cells in culture is evolving rapidly, and it may soon be feasible to test in randomized prospective fashion the concept of the in vitro phase II trial as a predictor of a drug's clinical behavior.

(*b*) Can the clinical results in a small subset of human tumor types predict clinical activity more broadly? In particular, can one use the results from clinical trials in a limited number of tumor types to determine whether further testing of an agent is warranted or not? Thus far, evaluable clinical studies with the agents represented in table 1 have revealed activity only in acute leukemias, the lymphomas, small cell lung cancer, and carcinomas of breast and ovary. Moreover, with the possible exceptions of dactinomycin and mithramycin, all drugs currently marketed in the United States for indications other than chronic myelogenous leukemia are active in at least one of these five tumor categories.

It might appear reasonable, then, to use these five tumors as a clinical screening panel; drugs negative after adequate trials in the panel would ordinarily not go on to further study. Exceptions could always be made for agents which were rationally synthesized for specific purposes (high lipophilicity), whose clinical development was motivated by particular findings in toxicology (streptozocin), or by studies of mechanisms of action (deoxycoformycin).

There are at least two significant problems in rigorously implementing a strategy such as this. The most compelling is the possibility of producing a self-fulfilling prophecy; using a clinical screening panel would leave little room for discovering newer classes of agents with a different spectrum of activity. At a time when we are prepared to bring drugs to clinical trial by novel selection procedures (eg, HTCFA or activity against human tumor cell lines), we should certainly allow for the outcome that some such agents may not conform to previous patterns.

Second, individual diseases in any tumor panel may become progressively less valuable in screening since

therapy for those diseases improves to the point where meaningful phase II trials become difficult or impossible. We probably have reached that point already with Hodgkin's disease, where phase II trials in patients who have failed fewer than seven to ten drugs cannot be done. Ovary cancer in the postcisplatin era may present analogous problems; although the success rate is certainly not so high as with Hodgkin's disease, patients coming to phase II studies tend increasingly to be very heavily pretreated and often have poorly measurable lesions.

In short, it seems premature to exclude many of the common epithelial cancers from routine phase II testing, even if past results have not been very productive.

Selection of Patients

About a decade ago, oncologists realized that a detailed description of patient characteristics within disease categories was as important in determining results as drug dose and schedule. This appreciation spelled the demise of the br ad phase II trial, at least in adult malignancies; as a byproduct, the writing of papers with the general title, "A Phase II Evaluation of Drug X in Disease Y," became a veritable growth industry. Although the past 10 years of phase II testing have certainly seen a few substantial successes, the landscape is littered with negative results.

It is certainly possible that drugs entering clinical trials over the past 5–10 years are inferior in anticancer activity to those of the 1960s. An equally valid additional (or alternative) explanation, however, is that, at least in those malignancies for which partially effective therapy exists today, the history of heavy pretreatment with chemotherapy prejudices our chances of obtaining accurate assessments of the antitumor potential of many active agents. Table 2 shows the response rate of several recently developed agents according to the pretreatment history of the patient population; it is quite clear that pretreatment with chemotherapy exerts a deleterious influence on the probability of response. Whether prior chemotherapy is independent of other potentially important prognostic variables such as performance status and extent of disease is much less clear; these variables may well be significantly correlated.

One might argue that we are in most need of drugs active against tumors resistant to current agents and hence testing in previously treated patients is desirable. Such testing, however, should not be the primary basis for evaluation of drug activity. Full-dose chemotherapy is often impossible in such patients and lack of activity in pretreated patients may not be a predictor of clinical usefulness in earlier disease.

The major point is that when a drug enters phase II trials, it should be tested in that patient group which is most likely to show a favorable effect provided that it is ethically permissible to do so; otherwise, the chances of missing the activity and potential usefulness of the drug are increased. Obviously, this criterion is best fulfilled by patients with maximum performance status, minimum extent of disease, and the minimum amount of prior therapy, especially chemotherapy, that ethical medical practice permits.

What are the ethical limitations here? Clearly, if potentially curative therapy exists, no one would responsibly suggest that an experimental drug of unknown efficacy be substituted for it. For most common malignant neoplasms in advanced stages, however, state-of-the-art drug treatment is not potentially curative; even when drug treatment offers striking short-term benefit, long-term control rates may be negligible.

In such situations, oncologists should be prepared to admit that new testing strategies are needed. Investigators who are committed to phase II drug testing should be prepared to enter patients with sensitive tumors who have failed one primary regimen (breast, small cell lung, or ovarian cancer; rhabdomyosarcoma; or non-Hodgkin's

TABLE 2.—Influence of prior treatment history on outcome

		No prior chemotherapy			Prior chemotherapy		
Disease	Drug	N	CR + PR	Confidence interval (80%)	N	CR + PR	Confidence interval (80%)
Colon cancer	Anguidine	18	4	10–39	63	4	3–12
	PALA	21	1	0.5–17	49	0	0–5
	Zorubicin	7	1	1.5–45	18	0	0–12
Melanoma	Chlorozotocin	78	12	10–22	110	6	3–9
Breast cancer	Mitoxantrone	64	19	22–38	250	18	5–10
	Vindesine	8	6	46–93	276	36	10–16
Lung cancer, small cell	Carboplatin	57	33	49–67	26	6	13–37
	Etoposide	22	10	30–61	135	21	11–20
Ovary	Carboplatin	68	34	42–58	33	7	12–33
	Cisplatin	44	29	55–76	225	88	35–44
Lung cancer, non-small cell	Vindesine	130	28	17–27	48	5	5–19

lymphoma). The literature is full of negative data for new drugs in these tumor types, and there is no way of ascertaining how many active agents have been consigned to the shelf because of poor patient selection.

In fact, for certain subgroups within these disease categories (slowly progressive metastatic breast cancer, extensive small cell lung cancer, stage IV ovary cancer, and indolent non-Hodgkin's lymphomas), the use of phase II agents as initial systemic therapy may be quite justifiable. A carefully monitored trial of a new agent, with change to a standard drug combination immediately upon disease progression or evidence of nonresponse, seems unlikely to prejudice chances of response to standard therapy, which is in any event of limited duration. The extent to which the nature of the initial treatment affects response rate and survival can be assessed by a trial design which randomizes patients to receive as first systemic therapy either a phase II agent or a standard combination; patients failing initial therapy are crossed over to the other treatment upon relapse. This design has been employed sporadically (9).

For the less-sensitive epithelial cancers (non-small cell lung cancer; epidermoid cancers of head and neck, cervix, and esophagus; colorectal cancer; and most of the soft tissue sarcomas), there is already widespread appreciation of the need to optimize characteristics of the patient population on phase II studies. A serious phase II effort in these disease categories should emphasize entry of patients with no prior history of exposure to cytotoxic agents.

These guidelines do not mean that heavily pretreated patients will be denied the potential benefits of new active agents. They do mean, however, that for a particular tumor type, new agents should be shown to be active in a favorable population of patients *before* they are given to a less favorable group. In view of the poor track record of the large majority of single agents in heavily pretreated patients with advanced disease, such a strategy makes very good sense. It will save patients with advanced, resistant disease from exposure to inactive agents from which the likelihood of toxicity is vastly greater than the chances of therapeutic benefit.

A related issue is the number of patients to be accrued in phase II studies. The recent literature contains many examples of overaccrual, particularly in the category of negative studies (10,11). Even for rather resistant tumors, a trial should probably be terminated once a response rate of 15%-20% can be excluded with a high degree of confidence. If an agent has exhibited promising degrees of activity, however, expanded accrual may be desirable, to estimate activity in subgroups of clinical interest. This information will be important in directing both the phase III evaluation and exploratory studies of new combinations.

Recent developments in biostatistical methodology have provided clinicians with the practical tools for establishing rational stopping rules (12,13). In addition, several cooperative groups have evolved the administrative sophistication that permits application of stopping rules in the context of a multicenter trial. There is no reason, therefore, why a trial cannot be stopped as soon as it has answered a question with the necessary degree of precision.

CONCLUSIONS

It seems clear that an overall re-evaluation of the way we conduct phase II evaluations of new drugs is in order. Until reliable in vitro tests exist for predicting clinical efficacy, we shall always be stuck with a certain amount of empiricism. A phase II effort which is directed initially toward those patients most likely to respond in each disease category will have the following desirable attributes.

(*a*) For an individual patient the probability of benefit from the new agent will be maximized and that of toxicity minimized.

(*b*) In the evaluation of the new drug, the chance of a false-negative result will be minimized. The cloud of uncertainty surrounding negative results will be at least partially dispelled.

(*c*) A truly inactive agent will be shown to be inactive after entry of the minimum number of patients. Two trials comprising 14-20 patients with no or minimal prior treatment are probably adequate for most agents. Thus, inactive new agents will not be given to more patients than necessary to establish inactivity.

If the phase II effort is to be redirected successfully in the manner outlined above, oncologists will have to acknowledge more clearly than in the past the very unsatisfactory nature of most current therapy for advanced cancer; the administration of a new drug of unknown efficacy as first or second systemic treatment is an explicit admission of this fact. In addition, they will have to see the clinical drug development program for what it should be—an attempt to discover and characterize new active agents—rather than for what it has in fact been to many over the past few years—an almost inexhaustible source of therapeutic alternatives for patients with heavily pretreated progressive cancer who have little or no chance of responding to new agents.

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Cyclic Alternating Chemotherapy for Small Cell Carcinoma of the Lung[1,2]

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Eighty-two previously untreated patients with small cell cancer of the lung were treated with six cycles of two alternating drug regimens: a new combination of mitomycin, methotrexate, and etoposide; and cyclophosphamide, doxorubicin, and vincristine. No maintenance chemotherapy was used. Consolidative thoracic irradiation and prophylactic cranial irradiation were employed. The median survival time for 32 limited-disease patients was 59 weeks, and for 50 extensive-disease patients was 35 weeks. Four-year survival was 12% for limited-disease patients and 2% for extensive-disease patients. These results were not superior to conventional combination chemotherapy regimens. [Cancer Treat Rep 69:1241–1242, 1985]

The three-drug combination of cyclophosphamide, doxorubicin, and vincristine (CAV) is a standard chemotherapeutic regimen for small cell cancer of the lung (SCCL) (1–3). There is theoretical evidence that alternating non-cross-resistant combinations of active drugs may diminish the probability of resistant tumor stem cells persisting (4). We report the results of alternating CAV with a new regimen consisting of mitomycin, methotrexate, and etoposide (MME). Since the component drugs in MME have different mechanisms of action from the agents in CAV, at least some non-cross-resistance was expected. Since MME produced short partial remissions in 30% of patients relapsing after treatment with CAV, we proceeded to test the CAV-MME alternation in a prospective fashion.

PATIENTS AND METHODS

Eighty-two previously untreated patients with biopsy or cytological proof of SCCL referred to the Cancer Control Agency of British Columbia between September 1979 and April 1981 were entered in this study. The pertinent patient characteristics are shown in table 1. Following a complete staging evaluation that included a serum biochemical profile, liver scan, bone scan, brain scan, and bone marrow aspirate and biopsy, 32 cases were classified as limited disease (LD) and 52 were classified as extensive disease (ED). LD was defined as tumor involvement confined to one hemithorax, the mediastinum, and ipsilateral supraclavicular nodes. Patients with pleural effusion (regardless of cytological findings) or disease more widespread than that described for LD were classified as ED.

Chemotherapy was started with the combination of mitomycin (10 mg/m^2 iv on Day 1), methotrexate (30 mg/m^2 iv on Day 1), and etoposide (80 mg/m^2 iv on Days 1, 2, and 3). This was alternated with cyclophosphamide (600 mg/m^2 iv), doxorubicin (60 mg/m^2 iv), and vincristine (1.4 mg/m^2 iv) at 3-week intervals, for a total of six cycles of chemotherapy. No maintenance chemotherapy was given.

Responding patients with LD received prophylactic cranial irradiation (3000 cGy in 10 fractions) after three cycles of chemotherapy. Upon completion of the planned six cycles of chemotherapy, all patients with LD were treated with consolidative irradiation (3000 cGy in 10 fractions) delivered to the site of prechemotherapy intrathoracic disease.

Patients with ED received prophylactic cranial irradiation and consolidative thoracic irradiation after chemotherapy only if a complete remission was attained.

RESULTS

Eighteen (56%) patients with LD had complete response at the completion of chemotherapy, and a further

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[4]We thank Lorraine Cho for typing the manuscript.

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TABLE 1.—Patient and response characteristics*

Characteristic	Patients with—	
	Limited disease	Extensive disease
Total patients	32	50
Sex (male/female)	25/7	34/16
Median age in yrs (range)	61 (37-78)	60 (40-73)
Performance status†		
0-2	29	42
3-4	3	8
Response rates (%)		
Complete response	22 (69)	11 (22)
Partial response (> 50% area reduction)	8 (25)	29 (58)
Disease progression (> 25% area increase)	2 (6)	10 (20)
Survival		
Median (wks)	59	35
2 yrs	21%	4%
4 yrs	12%	2%

*Unless otherwise specified, values = No. of patients.
†Eastern Cooperative Oncology Group criteria.

three patients attained complete response after consolidative thoracic irradiation. ED patients had a 22% complete response rate and a 58% partial response rate. The median survival time for 32 LD patients was 59 weeks, and 12% of this group survived 4 years. The median survival time for ED patients was 35 weeks, and 2% were alive at 4 years.

Nausea and vomiting was less frequent with MME (12%) than with CAV (60%). Anemia requiring transfusion was observed in 9% of patients, and leukopenia with fever occurred in 10%. Two patients died of sepsis. Interstitial pneumonitis occurred in five patients, with three episodes occurring shortly after treatment with MME. After receiving chemotherapy and radiotherapy, two patients with interstitial pneumonitis died of respiratory failure. The overall toxic mortality rate was 5%.

ED patients tended to relapse at the sites of their bulky disease. Seventy-six percent of the LD patients relapsed at systemic sites (56% at multiple sites) in this program using thoracic radiotherapy late in the treatment program.

DISCUSSION

The MME regimen is active in SCCL. However, mitomycin probably contributed to excessive myelosuppression and serious pulmonary toxicity. Consequently, we have deleted this drug from our current SCCL protocols. New mitomycin analogues with diminished toxicity must be carefully evaluated in this disease (5).

Although alternating chemotherapy forms the basis for many clinical trials in SCCL (6), and some investigators have suggested an advantage for this strategy (7,8), the actual clinical benefit proven thus far is marginal. The somatic mutation model specifies rigorous requirements that must be met before the utility of alternating sequence protocols can be demonstrated (4). The critical conditions are that the drug regimens be non-cross-resistant and quantitatively equivalent. Alternating chemotherapy with MME and CAV has not improved the treatment results for SCCL when compared to more conventional regimens, such as sequential CAV (1-3). While the MME combination is active in SCCL, its degree of non-cross-resistance and therapeutic equivalence to CAV is unknown.

The CAV and cisplatin-etoposide combinations may be better candidates for a test of the Goldie-Coldman hypothesis. Both regimens are highly active, and evidence, for at least partial non-cross-resistance, does exist (9). The National Cancer Institute of Canada is sponsoring trials testing this concept directly.

Cyclic alternating chemotherapy is a subtle and complex treatment strategy, and, although it is theoretically appealing, its beneficial application to a sinister neoplasm like SCCL is difficult and unproven. The ad hoc assemblage of multiple drug protocols relies too heavily on the time-consuming trial and error method. The guidance of appropriate mathematical models is essential.

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Comparison of Cyclophosphamide Plus Cisplatin Versus Hexamethylmelamine, Cyclophosphamide, Doxorubicin, and Cisplatin in Combination as Initial Chemotherapy for Stage III and IV Ovarian Carcinomas[1,2,3]

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Among 187 women with stage III and IV ovarian carcinoma who participated in this comparative clinical trial, 181 were eligible for analysis. Of these patients, 89 received monthly treatment with CP [cyclophosphamide (1 g/m^2) plus cisplatin (60 mg/m^2)] and 92 received monthly treatment with HCAP [hexamethylmelamine (150 mg/m^2/day × 7), cyclophosphamide (400 mg/m^2), doxorubicin (30 mg/m^2), and cisplatin (60 mg/m^2)]. All treatments were administered iv on Day 1 of each monthly treatment cycle, except for hexamethylmelamine, which was administered orally on Days 2–8. With a median follow-up time of 30 months, survival curves for the two treatment groups were almost identical, as were their times to progression [estimated median survival, 24.6 months (Kaplan-Meier)]. Patient characteristics which significantly influenced survival were age, degree of histologic differentiation, extent of residual disease, stage of disease, and histologic type. Results of posttreatment laparotomies have been equal for the two treatment groups. Toxic effects of the two regimens have been similar, except for more frequent, more severe, and earlier neurotoxicity among patients treated with HCAP. Of the two regimens, CP has the better therapeutic index. [Cancer Treat Rep 69:1243–1248, 1985]

Following the introduction by Wiltshaw and Kroner (1) of cisplatin to the chemotherapy of advanced ovarian carcinoma, the drug has been combined with other agents by many investigators seeking increased therapeutic benefits (2). In a previous randomized study, Mayo Clinic investigators demonstrated the clear therapeutic superiority of a combination of cisplatin and cyclophosphamide over cyclophosphamide alone (3). This result caused us to wonder whether a larger number of active agents together might produce even better results than those of our two-drug combination regimen in patients with stage III and IV ovarian carcinoma. Very favorable antitumor effects had been preliminarily described earlier by several groups of investigators in relation to the combination of hexamethylmelamine, cyclophosphamide, doxorubicin, and cisplatin (4–7). Thus, we developed a comparison between our two drugs and those four.

MATERIALS AND METHODS

Between April 1980 and September 1983, 187 women with histologically proven stage III or IV epithelial ovarian carcinoma agreed to participate in a randomized study comparing CP [cyclophosphamide (1 g/m^2) plus cisplatin (60 mg/m^2)] with HCAP [hexamethylmelamine (150 mg/m^2 daily × 7), cyclophosphamide (400 mg/m^2), doxorubicin (30 mg/m^2), and cisplatin (60 mg/m^2)]. All treatments were administered iv on Day 1 of each monthly treatment cycle, except for hexamethylmelamine, which was given orally on Days 2–8. The cisplatin was diluted in 1 L of 0.45% saline with 25 g of mannitol added and was infused iv over a 2-hour period. Each patient was scheduled to receive 12 monthly courses of treatment, with secondary laparotomy to follow at the end of 1 year if feasible and acceptable to the patient.

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[3]Presented at the 20th annual meeting of the American Society of Clinical Oncology, Toronto, Ontario, Canada, May 8, 1984.

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Chemotherapy doses were modified according to the levels of toxicity observed, with an intent to produce leukocyte count nadirs between 1500 and 2500/μl following each course of treatment. If necessary, re-treatment was delayed until the leukocyte count had recovered to 3500/μl.

All patients had an expected survival of at least 2 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or better. Patients with other active cancer problems, significant infection, active heart disease, or history of previous cancer chemotherapy or radiotherapy were excluded. Bone marrow, hepatic, and renal functions were demonstrated to be satisfactory by the presence of leukocyte counts of at least 4000/μl and platelet counts of at least 130,000/μl, the absence of increased direct reacting serum bilirubin, and the absence of serum creatinine > 1.5 mg/dl.

Prior to random allocation to one of the two treatment groups, the cases were stratified by age (≤ 49 vs ≥ 50 years), tumor histologic grade (well- or moderately well-differentiated vs poorly differentiated), ECOG performance status (0-1 vs 2-3), and extent of residual disease [none vs minimal (no mass > 2 cm in diameter) vs extensive (larger masses present, but < 250 g of total residual cancer) vs massive (≥ 250 g of total residual cancer)]. Each patient was observed monthly following randomization with interval medical history, physical examination, and chest x-ray plus standard biochemical and hematologic profiles. If disease progression was suspected but was not certain, computerized tomographic scans, ultrasound scans, etc were utilized for clarification of disease status as required.

Instructions concerning the primary and secondary laparotomies included the following: (*a*) description of unilateral or bilateral ovarian involvement; (*b*) description of all lesions found and locations throughout the peritoneal cavity (both lateral abdominal gutters, under surface of the diaphragm, omentum, cul-de-sac, and back of bladder); (*c*) pelvic and abdominal node involvement; (*d*) all involved sites to be excised if possible, and the largest para-aortic node to be excised even if not grossly involved; (*e*) peritoneal fluid cytology done immediately after opening the abdomen (saline irrigation specimen if no free fluid); and (*f*) an accurate description of the exact sites and sizes of any residual lesions before closing the abdomen.

In addition to continual protocol case monitoring by the North Central Cancer Treatment Group-Mayo Clinic statistical staff, all cases were reviewed and approved as valid by the Gynecologic Tumor Panel of our Pathology Committee.

In our analysis, the two treatment groups were compared with respect to duration of survival following randomization, time to disease progression, and objective response to treatment as determined by a comparison of the end-of-surgery description at pretreatment laparotomy with the beginning-of-surgery description at secondary (posttreatment) exploration. Ordinary clinical response and symptoms were not primary endpoints in this study because of their less precise nature. Toxic effects of the two regimens were also tabulated. Survival curves and time to progression curves were constructed using the Kaplan-Meier methods (8). The survival and time to progression durations for these two treatment groups were compared using the log rank test and the Cox partial likelihood score test (9). More generally, the stratified Cox proportional hazards model was employed to inspect the association of treatment with survival when adjusting for covariates (9). All P values are two-sided unless otherwise indicated. Interim analyses of the survival data were performed on an annual basis using the O'Brien-Fleming group sequential boundary as a guideline (10). Early termination of the trial did not occur. With the O'Brien-Fleming design, essentially no serial testing adjustment of the P values given here is required.

RESULTS

Among the 187 women who were randomized, only six were found to be ineligible. Three patients (undifferentiated sarcoma, colon cancer, and stage I ovarian cancer) were excluded from the CP treatment group. Of the three patients excluded from the HCAP group, one had fallopian tube cancer, one had metastatic breast cancer, and one had received radiation therapy prior to entering the study. Table 1 presents the entry characteristics by treatment for the 181 evaluable patients. The treatment groups were generally quite comparable with respect to each of these prognostic factors. Within each institution as well, the numbers of patients and their characteristics were similarly distributed between the two treatment groups.

With a median patient follow-up time of 30 months, survival curves for the CP and HCAP groups were almost identical, as were their times to disease progression (figs 1 and 2). Estimated median survival for the study population was 24.6 months, and estimated median time to progression of disease was approximately 16 months (Kaplan-Meier). These data are inconsistent, with HCAP yielding a 50% improvement over CP either in survival ($P = 0.019$) or in time to progression ($P = 0.033$). These are one-sided P values derived by employing the Cox partial likelihood score statistic to test for consistency of the data with a hazard ratio of 1.5.

The stratified Cox regression model was employed to assess the effect of treatment on survival, while adjusting for the effect of institution and of the variables in table 1. A 95% confidence interval obtained from this model suggests that the observed results are consistent with a treatment effect ranging from a hazard ratio (CP over HCAP) as high as 1.4 or as low as 1/1.6. (By a hazard

TABLE 1.—Distribution of eligible study patients according to patient and tumor characteristics by treatment group*

Characteristic	Treatment with— CP (*N* = 89)	HCAP (*N* = 92)
Median age in yrs (range)	60 (21-79)	58 (20-81)
⩽ 49	18	20
⩾ 50	71	72
Histologic differentiation		
Well-differentiated	11	8
Moderately differentiated	43	45
Poorly differentiated	35	39
Residual disease		
None	13	8
Minimal	37	42
Extensive	19	18
Massive	20	24
Performance score		
0-1	80	82
2-3	9	10
Stage of disease		
III	69	74
IV	20	18
Histologic type		
Serous	58	64
Mucinous	5	9
Endometrioid	9	8
Undifferentiated	14	11
Clear cell	3	0

* Unless specified otherwise, values = No. of patients.

ratio of 1.4, we mean that the estimated instantaneous death rate at each point in time for patients receiving CP is 1.4 times the rate for patients receiving HCAP. By a hazard ratio of 1/1.6, we mean that the instantaneous death rate at each point in time for patients receiving CP is 1/1.6 times the rate for patients receiving HCAP.)

Several factors have been studied for possible effects on survival within the entire study population. Table 2 reveals that age, degree of histologic differentiation, extent of residual disease at the initiation of chemotherapy, stage of disease, and histologic type significantly influence survival. Of particular interest is the 2-year survival rate of 86% for patients with no gross residual tumor and the 2-year survival rate of 84% for patients with well-differentiated tumors. In contrast, among patients with massive residual disease, only 24% were alive at 2 years, and the 2-year survival rate for patients with poorly differentiated tumors was only 42%. Survival at 2 and 3 years was also quite poor for patients with stage IV disease and for those with nonserous histology. Extent of residual disease at the beginning of treatment appears to be one of the most powerful prognostic discriminants, with considerable survival differences at 36 months among residual disease subgroups. While the overall trend is highly significant, survival comparisons of adjacent residual disease subgroups in table 2 reveal differences which are not yet significant, with two-sided log rank *P* values in the range of 0.10-0.16.

For interest, we have performed exploratory data analyses searching for significant interactive relationships between treatment and the various prognostic factors described above. We observed that while patients with good performance status survived equally well on either treatment, those with poor performance status (ECOG 2 and 3) seemed to survive longer receiving CP than if they received HCAP ($P = 0.003$) (fig 3). This same

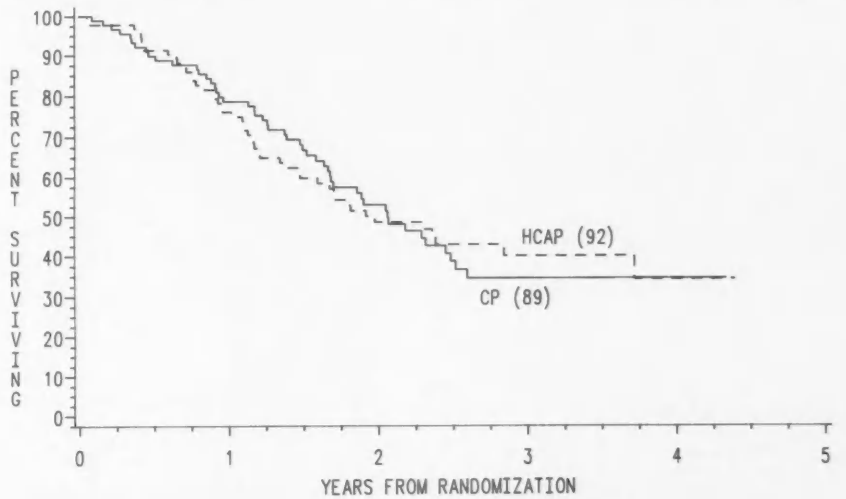

FIGURE 1.—Survival for patients treated with CP and HCAP.

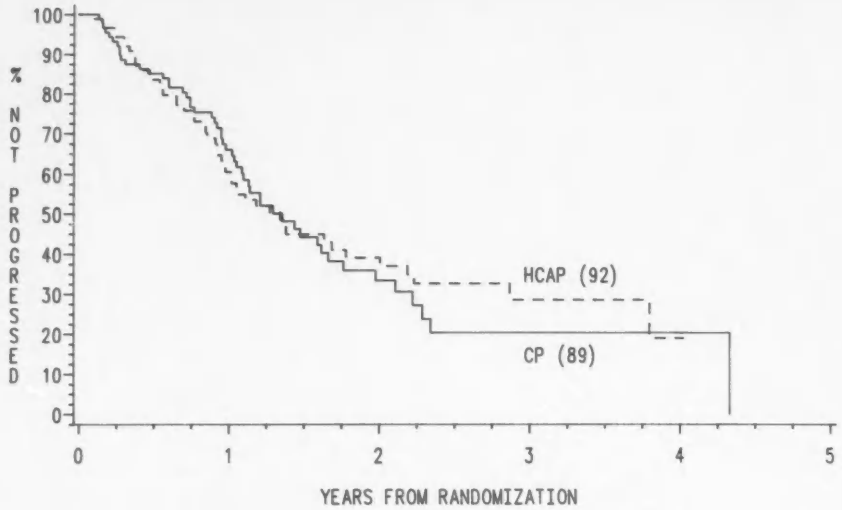

FIGURE 2.—Disease progression for patients treated with CP and HCAP.

type of observation was made in relation to residual tumor burden, with patients receiving CP surviving somewhat better than those receiving HCAP when massive residual disease was present ($P = 0.04$). We recognize that these associations discovered during exploratory subset analyses are less definitive than our primary data analyses.

During exploratory subgroup analyses in a previous Mayo Clinic study, the observation was made that young premenopausal women with massive residual disease

TABLE 2.—Survival estimates (Kaplan-Meier) of the eligible study population by patient characteristics

Characteristic	No. of patients	Survival (%) at — 12 mos	24 mos	36 mos	2-sided log rank *P* value
Age (yrs)					
⩽ 49	38	89	62	62	0.022
⩾ 50	143	74	48	32	
Histologic differentiation					
Well-differentiated	19	84	84	67	0.028
Moderately differentiated	88	77	50	35	
Poorly differentiated	74	76	42	31	
Residual disease					
None	21	90	86	64	< 0.0001
Minimal	79	80	58	48	
Extensive	37	76	49	31	
Massive	44	68	24	13	
Performance score					
0-1	162	79	52	38	0.21
2-3	19	63	37	37	
Stage of disease					
III	143	80	57	43	0.0003
IV	38	66	27	16	
Histologic type					
Serous	122	81	60	46	0.0003
Other	59	69	32	12	

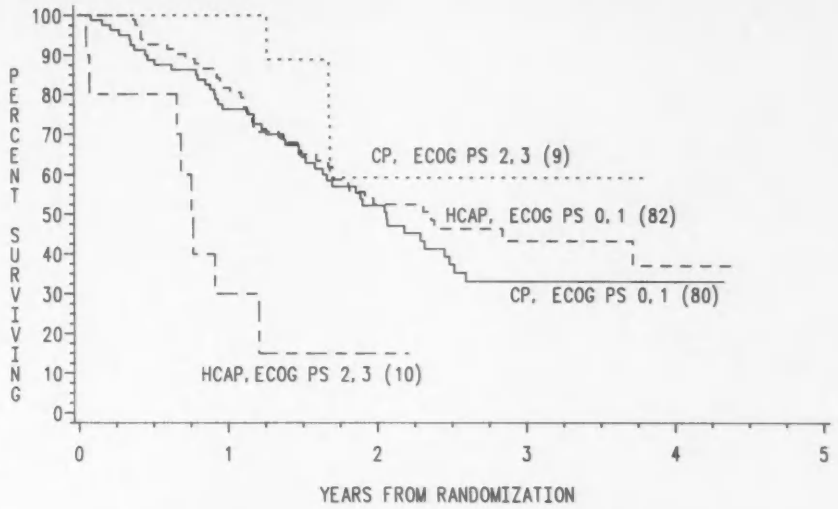

FIGURE 3.—Survival according to performance status for patients treated with CP and HCAP.

seemed to survive poorly as compared with older postmenopausal women with similarly massive tumor burdens (11). As a result, we looked for associations of this type in our present study population. All of our current analyses pertinent to this question indicate that young or premenopausal patients experience more favorable survival regardless of residual tumor burden when patients receive these cisplatin-based treatments.

Evidence of tumor regression at second-look surgery is another key measure of treatment efficacy in this disease. Among the 57 patients treated with CP and the 51 patients treated with HCAP who remained in the study at 1 year, 52 patients treated with CP and 45 patients treated with HCAP received secondary laparotomies. Following chemotherapy, 31 of the patients treated with CP and 26 of the patients treated with HCAP have had surgically proven objective tumor regression. Fourteen patients in each treatment group have been disease-free at second-look surgery, including two in each group who had no gross residual disease when treatment began.

Depth of myelosuppression has been similar following treatment with CP and HCAP, with median leukocyte and platelet count nadirs of 1300 and 101,000/μl and 1600 and 100,000/μl, respectively. Recovery from myelosuppression, however, was generally less prompt following the four-drug regimen, and a greater percentage of these patients experienced prolonged myelosuppression. This led to more frequent and longer treatment delays in patients treated with HCAP than among patients treated with CP. Neurotoxic effects have been apparent in patients treated with CP, but even more prominent following HCAP treatment (table 3). These effects have been more common, more severe, and have developed earlier in the course of treatment on the HCAP regimen. While 14 patients have developed (temporarily) disabling neurotoxic effects during the initial treatment year from HCAP, only one has been disabled by CP. Seven patients voluntarily withdrew prematurely from the assigned CP treatment regimen following a mean of 4.8 months, and 12 withdrew from HCAP after a mean of 4.3 months. Four other patients were removed from active treatment early because of toxicity (after 10 and 9 months with CP and after 9 and 6 months with HCAP). One other patient receiving HCAP was disqualified before completing 1 year of chemotherapy, for a major protocol violation. Two drug-associated deaths have occurred, an apparently allergic pulmonary edema episode following treatment with CP, and a severe myelosuppressive episode following treatment with HCAP in a patient with colonic obstruction.

DISCUSSION

Although several studies have identified the therapeutic superiority of combination chemotherapy over single alkylating agent treatments in advanced ovarian carcinoma, the selection of number of agents, the identities and doses of drugs to be included, and the optimal treatment schedule are still being debated (12). These present results and those of Bruckner et al (13) involving doxorubicin and cisplatin suggest that the optimal number of other agents to be combined with cisplatin currently might be one, since the additional toxic effects of the

TABLE 3.—Incidence, time of onset, and severity of neurotoxicity observed during treatment*

	CP (N = 89)	HCAP (N = 92)
Neurotoxic patients (%)	32 (36)	47 (51)
Median time to neurotoxicity (mos)	8.1	6.7
Level of severity (worst)†		
Mild	16	14
Moderate	15	19
Disabling	1‡	14§

* Unless specified otherwise, values = No. of patients.

†Mild = minor paresthesias present; moderate = troublesome symptoms without obvious loss of function; and disabling = clinically apparent loss of function (eg, impairment of ambulation, hand function loss, etc).

‡ Disabling paresthesias and numbness.

§ Disabling paresthesias and numbness (9 patients); disabling paresthesias and weakness (4); and disabling weakness (1).

third and fourth drugs generally have not been accompanied by survival gains beyond those achieved by two-drug regimens (12). Because of its superior therapeutic index, we consider the two-drug CP regimen preferable to the HCAP regimen for the initial treatment of stage III and IV ovarian carcinoma. Other investigators have recently presented pilot study results of cyclophosphamide-cisplatin combinations which appear to confirm the substantial therapeutic activity of this two-drug combination (14,15).

Encouraged by the improved efficacy of cisplatin when used in higher doses rendered more tolerable by hypertonic saline, investigators at the National Cancer Institute have begun a study of cyclophosphamide plus high-dose cisplatin in previously untreated patients with ovarian carcinoma (12). We eagerly await the results of that trial.

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Tastes Associated With Parenteral Chemotherapy for Breast Cancer[1,2]

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We employed a structured interview to retrospectively study tastes and vomiting associated with the parenteral components of cyclophosphamide, methotrexate, and 5-FU in 45 patients with stage II–IV breast cancer. Sixteen patients (36%) reported tastes which generally occurred in each cycle within 30 minutes of parenteral drug administration, lasted ≤ 1 hour, and were bitter. Five patients recalled that tastes seemed to produce vomiting. Tasting was significantly associated with postchemotherapy ($P < 0.01$) but not anticipatory vomiting. Employing logistic regression techniques, tasting did not significantly improve prediction of anticipatory vomiting by postchemotherapy vomiting. Tastes may be produced by the action of plasma or salivary cyclophosphamide, methotrexate, and 5-FU on taste buds. While tastes might cause some vomiting, they are not necessary for it. Because this was a retrospective study with a small sample, these findings require confirmation. [Cancer Treat Rep 69:1249–1251, 1985]

Abnormalities of taste are common in cancer patients (1). Recent reports suggest that tastes associated with chemotherapy administration serve as predictors of anticipatory nausea (2). Moreover, tastes might be conditioned stimuli actually causing some vomiting. Previously, we found that patients receiving adjuvant cyclophosphamide, methotrexate, and 5-FU (CMF) commonly developed anticipatory vomiting (3). In this study, we retrospectively studied tastes associated with CMF and their relationship to postchemotherapy and anticipatory vomiting.

METHODS

Two cross-sectional surveys of our clinic conducted 6 months apart identified 55 eligible patients. Patients were eligible if they were receiving or had received a CMF-containing regimen for stage II–IV breast cancer. Consenting patients underwent a brief structured interview administered by one of two investigators to assess tastes and postchemotherapy and anticipatory vomiting.

We assessed the frequency of tastes associated with the parenteral components of CMF. We inquired about the typical onset, duration, and quality of tastes and whether they produced vomiting. Patients estimated the usual frequency, duration, and intensity of postchemotherapy vomiting. We assessed the occurrence of anticipatory vomiting, defined as vomiting before and during drug administration.

Demographic, staging, and treatment data were obtained from the patient's chart. Statistical analysis included t tests, chi-square, and logistic regression.

RESULTS

Forty-five of 55 eligible patients were interviewed. Mean age was 51.5 (± 1.5 SE). Fourteen of 45 patients (31%) received CMF for metastatic disease; 31 (69%) received adjuvant CMF. Cyclophosphamide was administered orally to 33 patients (73%) and iv to 12 (27%). The median number of completed chemotherapy cycles at the time of the interview was six (range, two to 26 cycles). Thirty-two patients (73%) had completed CMF a median of 4 months prior to the interview (range, 1–14 months). Ten patients were not interviewed for the following reasons: five were not contacted; four were dead or dying; and one refused. They did not differ significantly from those patients interviewed according to age, extent of

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disease, or chemotherapy regimen.

Tastes associated with parenteral drug administration were reported by 16 patients (36%). Eleven of 16 patients (69%) reported tastes in each cycle. Thirteen patients (81%) reported the onset within 30 minutes of drug administration; ten (64%) within 5 minutes. Of 14 patients who could estimate taste duration, nine (64%) reported taste that lasted ≤ 1 hour. Eleven patients (69%) reported bitter taste. Five patients (31%) reported that the taste seemed to produce vomiting.

There were no significant differences between tasters and nontasters with respect to age, stage, number of chemotherapy cycles completed, or fraction who had completed CMF at the time of the interview. In the subset who had completed CMF, the interval from completion of CMF until the interview was no different for tasters and nontasters. Seven of 12 patients (58%) receiving iv cyclophosphamide reported tastes compared to nine of 33 (27%) receiving oral cyclophosphamide ($P > 0.1$).

Twenty-two patients (49%) reported postchemotherapy vomiting and 11 (25%) reported anticipatory vomiting during the course of treatment. Ten of 11 patients (91%) with anticipatory vomiting reported postchemotherapy vomiting compared to 12 of 34 (35%) who reported no anticipatory vomiting ($P < 0.005$).

Ten of 12 patients (83%) receiving iv cyclophosphamide reported postchemotherapy vomiting compared to 12 of 33 (36%) receiving oral cyclophosphamide ($P = 0.006$). Four of 12 patients (33%) receiving iv cyclophosphamide reported anticipatory vomiting compared to seven of 33 (21%) receiving oral cyclophosphamide ($P > 0.1$).

Twelve of 16 tasters (75%) reported postchemotherapy vomiting compared to ten of 29 nontasters (34%) ($P < 0.01$). Ten of 12 tasters (83%) with postchemotherapy vomiting averaged five or more vomiting episodes per treatment compared to two of nine nontasters (22%) ($P < 0.025$). One nontaster was unable to recall the average number of vomiting episodes per treatment. Employing logistic regression, we examined the relationship between postchemotherapy vomiting as the dependent variable and both taste and route of cyclophosphamide administration as independent variables. Both taste and route were significantly associated with postchemotherapy vomiting ($P < 0.05$).

Six of 16 tasters (38%) reported anticipatory vomiting compared to five of 29 nontasters (17%) ($P > 0.1$). Again employing logistic regression, we examined the relationship between anticipatory vomiting as the dependent variable and postchemotherapy vomiting, taste, and route of cyclophosphamide administration as independent variables. While postchemotherapy vomiting was a significant predictor ($P < 0.01$), the inclusion of taste and route of administration did not significantly improve prediction of anticipatory vomiting.

DISCUSSION

We focused on tastes and vomiting associated with parenteral components of CMF because we believed nausea as well as tastes and vomiting associated with daily oral cyclophosphamide would be more difficult to recall. Even with these precautions, recall error remains a possibility. Therefore, these findings require confirmation.

The pathogenesis of these tastes is unknown. The equal occurrence of tastes in patients receiving CMF as an adjuvant and for metastatic disease suggests that these tastes are not tumor-related. The association of tastes with postchemotherapy vomiting suggests that tastes may result from the tasting of vomited gastric contents. However, tastes were reported by four patients without vomiting, suggesting that this explanation is not sufficient to explain tasting. The occurrence of tastes soon after parenteral drug administration suggests that tastes are caused by CMF. Tastes may result from direct or indirect action of plasma or salivary CMF on taste buds (4,5). That patients receiving iv cyclophosphamide were more likely to be tasters than patients receiving it orally is consistent with this hypothesis. Patients receiving iv cyclophosphamide would be expected to have higher peak plasma and salivary concentrations than patients receiving it orally. Methotrexate and 5-FU in plasma or saliva may also contribute to tasting. Six of nine patients (67%) receiving oral cyclophosphamide who noted tastes did so within 5 minutes of parenteral methotrexate and 5-FU administration. Finally, genetic determinants of tasting might be investigated by examining the relationship between "tasting" CMF and phenylthiocarbamide.

The association of tastes and postchemotherapy vomiting suggests that tastes may be a cause of vomiting. Five of 16 tasters recalled that tastes seemed to produce vomiting. However, the finding that ten of 29 nontasters (34%) vomited suggests that tastes are not necessary to produce vomiting.

Finally, these data suggest that the occurrence of taste may add little to the occurrence of postchemotherapy vomiting as a predictor of anticipatory vomiting. A larger sample and logistic regression techniques would be required to exclude any contribution of tasting to the prediction of anticipatory vomiting.

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Cisplatin Bolus and 5-FU Infusion Chemotherapy for Non-Small Cell Lung Cancer[1,2]

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Patients with unresectable non-small cell lung cancer were treated with combination chemotherapy: cisplatin (100 mg/m²) on Day 1 and 5-FU (1 g/m² continuous infusion) on Days 1–5, initially every third week, then every 4–6 weeks. Group 1 consisted of 19 patients without prior therapy and Group 2 consisted of 15 patients with prior therapy. Using standard criteria, seven patients (37%) in Group 1 achieved partial remissions lasting 2 to > 31 months (median, 10). Patients with squamous cell carcinoma or good performance status were somewhat more likely to respond. Three patients (20%) in Group 2 achieved partial remissions lasting 5–7 months. Mucositis (grade II in six patients, grade III–IV in seven patients) was the dose-limiting toxicity, especially in Group 2. These responses to cisplatin bolus and 5-FU infusion in patients with non-small cell lung cancer were not greater than those achieved with other cisplatin-containing regimens. However, this combination does have activity and might be effectively combined with radiation therapy as has been done for carcinomas of other sites. [Cancer Treat Rep 69:1253–1255, 1985]

Successful chemotherapy of unresectable or metastatic non-small cell lung cancer remains an elusive goal, despite some activity for both single agents and combinations of drugs (1,2). To improve the likelihood of response, response duration, and survival, it is clear that more active drugs or drug combinations still need to be found. We were attracted to the combination of cisplatin bolus and 5-FU infusion by two observations. First, these agents have been shown to have impressive synergism in rodent tumor systems (3). When studied against L1210 leukemia in mice by Schabel et al (3), cisplatin and 5-FU (each of which alone only modestly prolonged median survival), when used together, resulted in a 60% disease-free long-term survival. Second, the combination of bolus cisplatin and continuous-infusion 5-FU given before definitive surgery or radiation therapy has been reported to have an objective response rate of 94% in patients with squamous cell carcinoma of the head and neck (4). Because of these observations, we initially used bolus cisplatin and 5-FU infusion to treat several patients with squamous cell carcinoma of the lung. Based on favorable responses observed in these patients, we began a prospective phase II trial in patients with unresectable non-small cell cancer of the lung.

PATIENTS AND METHODS

Patients with unresectable, histologically confirmed, non-small cell carcinoma of the lung were eligible for study. Patients were classified as having either adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma. Patients were eligible if they had either unresectable but limited disease (TMN stage III, M0), or metastatic disease. Patients could have had either no prior therapy or disease recurrent or progressive after prior therapy. Patients were required to have a performance status of at least 3 using Eastern Cooperative Oncology Group/Southwest Oncology Group criteria. Patients with either measurable or evaluable disease were included. Patients were required to have creatinine of < 2 mg/dl, wbc count > 4000/μl, platelet count > 100,000/μl, be free of active infection, have no significant impairment of hearing or peripheral nerve function, be geographically accessible for follow-up, and, after explanation of all potential therapeutic options, give informed consent to participate on forms approved by the Human Subjects Review Committee of the Virginia Mason Medical Center.

Between September 1981 and August 1983, 34 patients were studied. Of these, 19 patients (Group 1) with-

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TABLE 1.—Patient characteristics

	Group 1 (without prior therapy)	Group 2 (with prior therapy)
No. of patients	19	15
Median age in yrs (range)	63 (44-81)	58 (44-74)
Sex		
Male	14	10
Female	5	5
Performance status		
0	—	1
1	9	7
2	7	4
3	3	3
Histology		
Adenocarcinoma	8	8
Squamous cell carcinoma	10	6
Undifferentiated carcinoma	1	1
Stage		
III	5	2
IV	14	13

out prior therapy and 15 patients (Group 2) with prior therapy were treated after developing recurrent or progressive tumor. Patient characteristics, including age, sex, performance status, histology, and stage of tumor are given in table 1. Of the patients who had received prior therapy, eight had received prior radiotherapy only, two had received prior chemotherapy only, and five had received both radiotherapy and chemotherapy.

Chemotherapy was administered initially every 3 weeks for three courses, then every 4 weeks for three courses, and then every 6 weeks thereafter. Patients were admitted to the hospital, hydrated with at least 1 L of fluid (generally 5% dextrose in one-fourth normal saline plus 20 mEq KCl), and then, if the patient had voided at least 500 ml, given cisplatin (100 mg/m^2) in normal saline over 1 hour, followed by at least an additional 2 L of fluid. A five-drug antiemetic regimen consisting of prochlorperazine, dexamethasone, diphenhydramine, metoclopramide, and diazepam was utilized. 5-FU was begun 2 hours after the cisplatin and was generally administered at a dose of 500 mg/m^2 in 500-1000 ml of 5% dextrose in one-fourth normal saline given every 12 hours times ten doses as a continuous infusion. Once started, any delays in infusion were "made up" so as not to prolong the overall period of the infusion.

Cisplatin bolus and 5-FU infusion chemotherapy were generally continued until patients developed evidence of progressive disease or unacceptable toxicity. However, for patients with unresectable but limited disease who had not had prior therapy, response status was carefully documented after three cycles of chemotherapy. A course of radiation therapy designed to encompass all known disease was then administered, generally 5000-6000 rad. If, on the day chemotherapy was due, the wbc count was $< 3000/\mu l$, the platelet count was $< 100{,}000/\mu l$, or recovery from mucositis was still incomplete, the next treatment course was delayed at least 1 week or until toxicity subsided. Mucous membrane toxicity was defined as follows: *grade I*—erythema; *grade II*—ulceration, able to eat; *grade III*—ulceration, unable to eat; and *grade IV*—hospitalization required for parenteral fluids and/or pain control.

Complete remission was defined as the disappearance of all clinical evidence of active tumor for a minimum of 4 weeks; partial remission was defined as a $\geq 50\%$ decrease in the measured or estimated sum of the products of bidimensional diameters of measurable or evaluable lesions. Minimal response was defined as a definite decrease in tumor size which failed to satisfy criteria for partial remission. Remission and survival times were determined from the date of the initial course of chemotherapy. All patients who received one course of chemotherapy are included.

RESULTS

Of the 19 patients in Group 1, none achieved a complete remission; seven achieved partial remissions; three achieved minimal responses; and nine demonstrated no response to the chemotherapy regimen. Partial remissions were achieved after one to three cycles of chemotherapy (median, two). One of the eight patients with adenocarcinoma achieved a partial response; six of the ten patients with squamous cell carcinoma achieved partial responses; and the single patient with undifferentiated carcinoma did not achieve a partial response. These results are suggestive of greater responsiveness among patients with squamous cell carcinoma ($\chi^2 = 1.9$, $P < 0.2$).

Five of the nine patients with a performance status of 1, two of the seven patients with a performance status of 2, and none of the three patients with a performance status of 3 achieved partial remissions. These results suggest an improved response rate among patients with a performance status of 1 ($\chi^2 = 1.3, P < 0.2$). Disease stage did not appear to be related to response, since partial remissions were achieved by one of the five stage III patients and by six of the 14 stage IV patients.

Of the seven patients who achieved partial remissions, four had residual disease which could be encompassed in a single irradiation field. These four patients received three cycles of chemotherapy followed by radiation therapy and then did not receive chemotherapy following radiation therapy. Three patients progressed at 7, 10, and 12 months after initiation of therapy and one remains free of recurrent tumor after 31 months. Of the other three patients to achieve a partial remission, one refused to continue therapy after his first cycle and relapsed at 2 months, one relapsed at 6 months while continuing

chemotherapy, and one received six cycles of chemotherapy which was then discontinued because of drug toxicity and then relapsed at 16 months.

Thus, seven (37%) patients in Group 1 achieved partial remissions, with a duration of 2 to > 31 months (median, 10) from the initiation of therapy and 1 to > 29 months (median, 8) from the time the partial remission was achieved. The overall survival of Group 1 patients was 2 to > 31 months (median, 6).

Among the patients in Group 2, three (20%) achieved partial remissions, five had minimal response or stable disease, and seven had no response or progressive disease. Of the patients who achieved partial remissions, two had disease progression at 5 and 6 months at the original sites of disease, and one had disease progression at 7 months in the central nervous system. Survival of the Group 2 patients was 2 to > 33 months (median, 6).

Mucositis was the most significant toxicity observed: grade I in five patients, grade II in six patients, and grades III–IV in seven patients. Mucositis was more prominent in patients in Group 2, ie, five of the seven patients with grade III–IV toxicity were among the patients who had received prior therapy and these five patients represented one-third of the patients in Group 2. Alopecia and phlebitis were both common. Ototoxicity was observed in four patients, two mild and two severe; this required the discontinuation of cisplatin after one and five cycles of therapy. Significant peripheral neuropathy was observed in two patients, while leukopenia (wbc count = 1900/μl with 40% granulocytes), truncal rash, renal failure, and 5-FU cardiac toxicity were each observed in single patients.

DISCUSSION

The likelihood of partial remission (37% in previously untreated and 20% in previously treated patients) and the duration of the remissions (median, 10 and 6 months, respectively) achieved in this study with cisplatin bolus and 5-FU infusion indicate that this drug regimen has activity in patients with unresectable non-small cell lung cancer. The administration of 5-FU by infusion for 5 days requires either hospitalization or an established institutional mechanism for administration of continuous-infusion outpatient chemotherapy. Thus, this chemotherapy regimen is inconvenient and expensive. Hence, general acceptance of this regimen would require that clinical results be substantially better than those achieved with more convenient drug regimens. The activity observed, however, is limited and not superior to that achieved with other cisplatin-containing combinations (1,2).

We did confirm the lack of myelosuppression associated with cisplatin bolus and 5-FU infusion chemotherapy (4,5). This suggests that it would be feasible to add to this regimen a myelosuppressive drug active against non-small cell lung cancer. Possibilities include ifosfamide, doxorubicin, mitomycin, or vinblastine (6). Because of the substantial mucositis observed with 5-FU infusion for 120 hours in this study, particularly in patients who had received prior irradiation or chemotherapy, we would suggest that 5-FU infusion be limited to 96 hours, particularly in patients with prior therapy.

Cisplatin bolus and 5-FU infusion chemotherapy have been given *concurrently with radiation therapy* with impressive results in patients with squamous cell carcinoma of the esophagus (5) or cloacogenic/anal carcinoma (7,8). There are additional data indicating significant potential synergism between cisplatin and radiation therapy in both experimental tumor (9,10) and clinical (11) systems. These considerations, plus the activity demonstrated in this study for cisplatin bolus and 5-FU infusion in patients with non-small cell lung cancer, suggest the possibility of using cisplatin, 5-FU infusion, and concurrent radiation therapy in the treatment of patients with advanced but still localized non-small cell lung cancer.

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Consecutive Dose-Finding Trials Adding Lorazepam to the Combination of Metoclopramide Plus Dexamethasone: Improved Subjective Effectiveness Over the Combination of Diphenhydramine Plus Metoclopramide Plus Dexamethasone[1,2]

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Four consecutive trials were undertaken to study lorazepam at each of three dosage levels and diphenhydramine when used in combination with iv metoclopramide and dexamethasone in patients receiving cisplatin at 120 mg/m^2. The combination containing diphenhydramine had been the most effective treatment identified in prior trials. Earlier studies have found lorazepam to be a useful adjunct to other antiemetic agents. Sixty-five patients who had never received chemotherapy or antiemetics were directly observed in the hospital for 24 hours following cisplatin. Overall, 56% of the patients experienced no emesis and 78.5% of the patients had two or fewer vomiting episodes during the study period. No significant differences were noted in the number of patients who experienced no emesis or two or fewer episodes among the four trials. More sedation was seen with the lorazepam-containing regimens; other side effects were similar in type and severity. The trial using the highest dose of lorazepam (1.5 mg/m^2) demonstrated significantly greater patient satisfaction ($P = 0.039$) and less anxiety during therapy ($P = 0.02$) when compared with the diphenhydramine combination. We conclude that combinations of iv metoclopramide plus dexamethasone with either diphenhydramine or lorazepam are well tolerated and effective in controlling cisplatin-induced emesis. The regimens containing lorazepam produced better subjective evaluations, and the combination using the highest lorazepam dose tested showed superior patient satisfaction and less anxiety during therapy. [Cancer Treat Rep 69:1257–1262, 1985]

Both high-dose iv metoclopramide (1–5) and dexamethasone (6–8) have been shown to be safe and effective single agents for the control of emesis caused by anticancer chemotherapy. Improved antiemetic control and lessened side effects have been observed when metoclopramide and dexamethasone were used in combination (9–11). Even so, the control of vomiting is not complete in all patients and the chemotherapy experience remains a difficult obstacle in cancer therapy. The search continues for additional agents to combine with the existing drugs and combinations to further improve the control of vomiting and side effects caused by both the chemotherapeutic and antiemetic agents.

Lorazepam is a benzodiazepine used widely as a premedicant for surgery and to treat anxiety. Doses of lorazepam up to 4 mg/m^2 iv have been safely given and have been found to cause the maximal impairment of patient recall (12). Several encouraging studies have reported that lorazepam is useful as an adjunct to other antiemetic agents (13,17). Trials using lorazepam as a single agent for the control of chemotherapy-induced emesis have also been undertaken (18–20). Although only limited antiemetic activity was noted, major side effects were rare, the drug was well accepted by patients, and it

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appeared to lessen the anxiety caused by anticancer chemotherapy.

This report details the results of consecutive, open-label trials designed to investigate the dose of iv lorazepam used in combination with high-dose iv metoclopramide plus dexamethasone for the control of vomiting and other effects caused by high-dose cisplatin. Earlier trials have demonstrated that doses of lorazepam up to 2 mg/m^2 could be safely given to patients receiving cisplatin (20). However, excessive sedation and urinary incontinence were common at the highest dose. The initial lorazepam dose used in these trials (1 mg/m^2) had been shown to be safe and to produce improved subjective control of emesis (20). Dosages were escalated by 25% and then 20% to see if a dose-response relationship existed for both the advantageous and toxic effects of lorazepam when used in combination. Moreover, since prior trials suggested that the primary advantages of lorazepam would be improved patient acceptance and lessened anxiety related to cisplatin administration, both subjective and objective measurements of antiemetic efficacy and adverse effects were made.

PATIENTS AND METHODS

From December 1983 to August 1984, 65 patients with histologically confirmed cancer were entered. Only patients who had not previously received chemotherapy and who had a Karnofsky performance status of $\geq$ 60% were eligible. As required for the concurrent chemotherapy protocols, each patient had a wbc count > 4000/mm^3, a platelet count > 120,000/mm^3, serum creatinine < 1.9 mg/dl and serum bilirubin < 2.0 mg/dl. All patients were hospitalized to receive cisplatin at a dose of 120 mg/m^2 of body surface area in a 20-minute iv infusion. Cisplatin treatment followed vigorous iv hydration with mannitol diuresis as previously described (1). Patients with non-small cell lung cancer also received vindesine (3 mg/m^2) or vinblastine (5 mg/m^2), agents that generally do not induce emesis (21,22). Eighty percent of individuals with lung cancer were also given mitomycin, an agent reported to rarely cause severe vomiting (23).

All patients (Trials I–IV) received both metoclopramide and dexamethasone iv. Iv dosages of metoclopramide (Reglan, A. H. Robins, Richmond, VA) were diluted in at least 50 ml of 0.9% sodium chloride and infused over 15 minutes. Metoclopramide was given at a dose of 3 mg/kg for a total of two doses, given 30 minutes prior to cisplatin and 1 1/2 hours afterward. Dexamethasone was given as an infusion over 5 minutes in a single 20-mg iv dose 35 minutes prior to cisplatin. The dose and schedule of both metoclopramide and dexamethasone used were the optimum ones determined for this combination in prior trials (10).

In Trial I, diphenhydramine was given in a single 50-mg iv dose 45 minutes prior to cisplatin, in addition to the dexamethasone and metoclopramide. This three-drug combination was the most effective in a previous series of consecutive trials. Additionally, this dose and schedule of diphenhydramine had been found to be the most convenient and effective one when combined with metoclopramide and dexamethasone (10). Eighty-one percent of 42 patients receiving cisplatin had no emesis and 93% had two or fewer emetic episodes in prior trials of this regimen (10).

In Trials II, III, and IV, lorazepam (Ativan, Wyeth Laboratories, Philadelphia, PA) was given by slow iv injection (over 5 minutes), 45 minutes prior to cisplatin administration and every 4 hours afterward for a total of three doses, if side effects permitted. The doses of lorazepam used in Trials II, III, and IV were 1.0 mg/m^2, 1.25 mg/m^2 and 1.5 mg/m^2, respectively. The maximum single dose given in any trial was 3.0 mg/m^2. Metoclopramide and dexamethasone were given in exactly the same way as in Trial I.

Food or fluids by mouth were not allowed during the initial 12 hours of all trials; no sedative or other antiemetic drugs were given 10 hours before the study or during the study. Patients who had antiemetic benefit were offered the same regimen during subsequent chemotherapy.

The number of episodes of emesis was recorded for each patient. Any vomiting productive of liquid was recorded as an emetic episode. In addition, one to five retches (vomiting not productive of liquid) within any 5-minute period were also counted as a single emetic episode. All patients were directly observed in the hospital for 24 hours after cisplatin administration. Side effects of treatment were also directly observed and recorded: sedation, number of bowel movements, the occurrence of akathisias, acute dystonic reactions, and urinary incontinence. Sedation was graded as follows: *none; mild* (patient lethargic but aroused by verbal stimuli and completely oriented to time, place, and person when awakened); *moderate* (patient aroused only by physical stimuli and completely oriented when awakened); and *marked* (patient aroused only by physical stimuli and disoriented when awakened). Patients were awakened if necessary and side effects assessed before each dose of study medication, at the conclusion of the 24-hour observation period, and at least every 3 hours during the trial. Diarrhea was defined as greater than three loose bowel movements during the 24-hour observation period. All patients were asked whether or not they remembered receiving their chemotherapy.

At the completion of the 24-hour study period, all patients gave their assessment of antiemetic control and side effects. By means of a 100-mm visual analogue scale (24), patients estimated the degree of emesis, nausea, comfort, satisfaction, sleepiness, and anxiety they experienced. All patients were asked whether they wished to receive the same antiemetic therapy again if

they received cisplatin-containing chemotherapy in the future. Thirty minutes after completion of the assessment, patients answered the same questions asked in a different order. Overall, for each visual analogue scale (emesis, nausea, comfort, satisfaction, sleepiness, anxiety during treatment, and "anxiety now"), there were no significant increases or decreases between the first and second administrations of the questionnaire. The median changes were 0, 0, 0, 0, 0.5, 0, and 3.5 mm, respectively. Sixty-five percent of the changes observed were strictly < 10 mm, and the median absolute deviations were 3, 4, 5, 3, 2, 8, and 9 mm, respectively.

Estimates of nausea and vomiting occurring during the 4 days following the study period were also obtained. Patients were contacted daily (by telephone or in person) and asked about the presence or absence of *any* nausea or emesis (as defined above) during the 96 hours following the 24-hour in-hospital observation period. All participants were also asked to keep a written log noting the occurrence of any nausea or vomiting. At discharge, patients were given prescriptions for oral prochlorperazine (10–20 mg) to be taken on an as-needed basis. No other antiemetics were routinely prescribed.

Statistical analysis.—Pearson's chi-square test was used to compare the frequencies of the observations collected. For each observed response, the results of the individual trials were compared to each other. To compare the results of the subjective assessment (visual analogue scale scores), a two-sample t-test was employed.

RESULTS

The characteristics of the 65 patients entered into the trials are shown in table 1. All entered patients were evaluated for objective antiemetic responses and side effects, and each received full dosages of metoclopramide, dexamethasone, and the initial dosages of lorazepam and diphenhydramine as planned. Thirty-seven percent of the patients received a second dose of lorazepam and no patient received a third dose. Subsequent lorazepam dosages were held in each case because of moderate sedation resulting from prior doses of the antiemetic regimens. Table 2 displays the antiemetic and toxic effects observed in the four trials. The proportion of patients experiencing no emesis ranged from 38% to 69% and the proportion having two or fewer vomiting episodes ranged from 69% to 94%. There were no significant differences in the number of emetic events observed among the four treatment regimens.

The number of patients experiencing sedation was significantly higher ($P < 0.001$) in the lorazepam-containing treatment regimens when they were compared to the regimen containing diphenhydramine either individually or when all lorazepam-containing regimens were combined. Only one patient (2% overall) experienced marked sedation (disoriented when awakened). Among the three trials examining differing lorazepam dosages, no significant differences in sedation were seen ($P = 0.111$). Diarrhea was more common in Trial I (31%) than in Trials II (0%), III (6%), or IV (6%) ($P = 0.02$).

No significant differences among the four treatment regimens were observed overall when the incidence of acute dystonic reactions ($P = 0.12$), akathisias requiring therapy ($P = 0.412$), urinary incontinence ($P = 0.794$), or memory of chemotherapy administration ($P = 0.06$) was compared. Two acute dystonic reactions were observed among the 65 patients treated (overall incidence, 3%). Both reactions occurred in men in Trial IV (one age 30

TABLE 1.—Patient characteristics*

	Trial—			
	I	II	III	IV
	Diphenhydramine + metoclopramide + dexamethasone	Lorazepam (1.0 mg/m^2) + metoclopramide + dexamethasone	Lorazepam (1.25 mg/m^2) + metoclopramide + dexamethasone	Lorazepam (1.5 mg/m^2) + metoclopramide + dexamethasone
Patients entered	16	16	16	17
Age (yrs)				
Mean	55	54	55	53
Range	39–69	38–62	38–72	30–66
Sex (M:F)	6:10	11:5	10:6	16:1
Performance status				
80% + 90%	13	15	15	17
60% + 70%	3	1	1	0
Site of primary cancer				
Lung	16	15	15	14
Other	0	1	1	3

* Unless otherwise specified, values = No. of patients.

TABLE 2.—Observed antiemetic results and side effects

	Trial—			
	I	II	III	IV
	Diphenhydramine + metoclopramide + dexamethasone	Lorazepam (1.0 mg/m^2) + metoclopramide + dexamethasone	Lorazepam (1.25 mg/m^2) + metoclopramide + dexamethasone	Lorazepam (1.5 mg/m^2) + metoclopramide + dexamethasone
No. of patients	16	16	16	17
Percent of patients with:				
0 emetic episodes	56	38	69	59
0,1, or 2 emetic episodes	69	75	94	76
Sedation				
None	38	0	0	0
Mild	62	31	6	6
Moderate	0	69	88	94
Marked	0	0	6	0
Diarrhea*	31	0	6	6
Acute dystonic reactions	0	0	0	12
Akathisia	0	0	0	6
Urinary incontinence	0	6	6	6

*Greater than 3 loose bowel movements.

and one age 48). The reactions cleared completely within 5 minutes following an iv injection of 50 mg of diphenhydramine. Five individuals (8%) complained of transient restlessness that subsided spontaneously and did not require therapy. None of the three individuals (all of whom had received lorazepam and were undergoing forced diuresis with mannitol) who experienced urinary incontinence complained of this symptom, and it did not recur after the sedation induced by the antiemetic regimen subsided. All of the patients who received diphenhydramine (Trial I) remembered receiving their chemotherapy; 71%–88% of the patients who received lorazepam remembered receiving their chemotherapy. The number of observed vomiting episodes was not related to the patient's ability to remember the administration of chemotherapy. No ataxia, dizziness, hypotension, dysphoria, hyperglycemia, fluid retention, slowed respiration, or hallucinations were observed.

Subjective evaluations of efficacy and adverse effects of the four regimens tested were available from 61 patients (94%), and are depicted in table 3. Three individuals refused to complete the questionnaire and one non-English-speaking patient could not complete the form at the required time because of the lack of an interpreter. When the four trials were compared, less "anxiety now" was reported among patients who had received lorazepam ($P = 0.019$). Trial IV, which utilized the highest tested dose of lorazepam (1.5 mg/m^2), had more satisfaction ($P = 0.039$) and sleepiness ($P = 0.05$) and less anxiety during therapy ($P = 0.02$) when compared to Trial I, which contained diphenhydramine. There were no significant differences in any of the median visual analogue scale measurements among the three lorazepam-containing regimens. The percentage of patients who wished to receive the same antiemetic regimen again the next time they received cisplatin ranged from 93% to 100% among the four regimens studied ($P = 0.814$).

Estimates of the presence or absence of any nausea and emesis occurring after the 24-hour study period (delayed emesis) were made by daily retrospective interviews and a mail-in questionnaire. Such information was available from 41 patients. Vomiting occurred in 76% and nausea occurred in 83% of the patients during the 4-day interval following the 24-hour observation period. The incidences of both delayed nausea and vomiting were greatest from 48 to 72 hours after cisplatin. The incidence of delayed emesis or nausea did not differ significantly among the four trials, either overall or for any 24-hour period evaluated. Patients generally described the phenomenon of delayed emesis or nausea as mild and it did not interfere with their ability to maintain adequate hydration.

DISCUSSION

The results of these four consecutive trials again demonstrate that combinations containing high-dose iv metoclopramide and dexamethasone are well tolerated and effective in controlling vomiting following cisplatin administration (9–11). They further confirm the safety and high patient approval of lorazepam when used in combination with other antiemetic agents (13–17,19).

These trials employed the same methods used in the previous studies at our institution (1,10). All patients received the same dosage of cisplatin, were directly observed in the hospital for 24 hours, and had no previous exposure to either antiemetic agents or cytotoxic chemo-

TABLE 3.—Patient subjective evaluations of antiemetic and side effects using a questionnaire and a 100-mm visual analogue scale

	Trial—			
	I	II	III	IV
	Diphenhydramine + metoclopramide + dexamethasone	Lorazepam (1.0 mg/m^2) + metoclopramide + dexamethasone	Lorazepam (1.25 mg/m^2) + metoclopramide + dexamethasone	Lorazepam (1.5 mg/m^2) + metoclopramide + dexamethasone
No. of patients	16	16	16	17
Mean measurements of visual analogue scales (mm)*				
Emesis	21	28	17	11
Nausea	27	31	22	10
Comfort	62	71	73	72
Satisfaction	71	78	85	91
Sleepiness	58	64	67	76
Anxiety during therapy	58	47	46	30
"Anxiety now"	49	30	21	36
Percent of patients remembering chemotherapy administration	100	88	67	71
Percent of patients wanting same treatment again	93	93	100	94

* 0 = the least; 100 = the most.

therapy. Cisplatin was chosen as the emesis-producing agent for study because of its widespread use, efficacy in combination in the treatment of several cancers (25,26), and the severity and predictability of the nausea and vomiting it produces (median of 10.5 vomiting episodes in 24 hours) (1,25–27).

The number of patients experiencing no emesis or two or fewer episodes of vomiting did not differ significantly among the four regimens tested. Although moderate sedation was more common among the lorazepam-containing regimens, it did not interfere with medical care or patient comfort. Overall, each of the four regimens was well tolerated and well accepted by patients, as evidenced by the observed visual analogue scale scores and the desire of > 92% of the patients to receive the same antiemetic treatment again. Median observed scores for nausea, comfort, emesis, satisfaction, and anxiety were consistently better for the lorazepam-containing regimens that also exhibited greater sedation. Trial IV using lorazepam at the highest dose of 1.5 mg/m^2 demonstrated significantly more satisfaction and sleepiness and resulted in less anxiety during therapy when compared to Trial I, which combined diphenhydramine with metoclopramide and dexamethasone. Based on the superior subjective evaluations and comparable objectively measured efficacy and side effects, the combination of lorazepam given at the highest tested dose of 1.5 mg/m^2 with metoclopramide plus dexamethasone was considered the best of all studied regimens.

An attempt was made to estimate the occurrence of nausea and vomiting following completion of the trial, a time when antiemetic effects of the study drugs were not expected. Because delayed emesis usually occurs outside the hospital, it was not possible to directly observe the patients and record the number of emetic events as we did during the 24-hour study period. The majority of patients developed the delayed onset of emesis and nausea. At present, there is no proven treatment to control delayed vomiting and no studies have been conducted to investigate this problem.

The conclusions of this report are the product of the comparison of the results of consecutive trials, each designed to determine the efficacy of an antiemetic combination and to define toxic effects. These data are encouraging and support the initiation of randomized trials comparing these regimens against active single agents or against other active combinations of agents.

Combinations of high doses of iv metoclopramide and dexamethasone with either diphenhydramine or lorazepam are safe and effective in controlling emesis caused by the administration of cisplatin. Although all regimens tested were similar in the degree of objective emetic control and type and degree of side effects observed, the lorazepam-containing regimens, and the highest dose of the lorazepam regimen in particular, consistently demonstrated better patient evaluations of effec-

tiveness and improved satisfaction over the diphenhydramine-containing combination.

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Tolerance to Antineoplastic Agents in Children and Adults[1]

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Although malignancies of children and adults are quite different in their origins, embryonal tumors and sarcomas being more common in the young than in adults, the spectrum of activity of antineoplastic agents embraces both populations. Childhood malignancies occur far less frequently, accounting for only 3% of all cancer (1), and are generally more responsive to chemotherapy than adult tumors (2). Nonetheless, while many patients with childhood cancer may be curable, other pediatric patients continue to be resistant to current chemotherapy regimens. The search for effective new drugs therefore remains an important part of experimental chemotherapy in children.

The low incidence and high responsiveness of childhood cancer greatly influence the way new drugs are evaluated in this population, since accrual to experimental clinical trials is dependent upon the number of patients with refractory or intractable disease. An extensive drug development program sponsored by the National Cancer Institute (NCI) brings approximately six new drugs to clincal evaluation each year. An average of four to six dose-seeking trials (phase I) are conducted for each drug in the adult population to define the maximum tolerated dose (MTD) in the best schedule. Separate phase I trials are generally conducted in patients with leukemia and solid tumors, since myelosuppression is not considered dose-limiting in the presence of marrow disease. Given the relatively small number of pediatric cancer patients, to duplicate such an effort in children would be impossible and unnecessary unless substantial differences in toxicity patterns or dose tolerance were observed between the two populations. It is widely recognized, however, that children handle antibiotic and antiepileptic drugs differently from adults (3–5), and preliminary data concerning antineoplastic agents are similarly suggestive (6). New data on several compounds recently evaluated in phase I trials in children permit further comparison of the toxic effects seen in children with those noted in adults. We have therefore analyzed the results of adult and pediatric phase I trials of 17 experimental anticancer drugs in an attempt to more clearly define the qualitative and quantitative toxicity differences between these two populations. We have also outlined a new procedure design for phase I trials in children.

MATERIALS AND METHODS

The data base sources are as follows: (*a*) for drugs entered in clincal trial prior to 1980, publications from a computer-generated bibliography of phase I trials in children and adults; and (*b*) for more recently developed drugs, the Clinical Trial Monitoring Service data base, a computerized data base that captures demographic, toxicity, and response data of all patients entered in phase I trials with drugs introduced by the NCI since 1980.

Drugs were selected for analysis if (*a*) independent phase I trials were conducted in children and adults; (*b*) separate MTDs were established for solid tumors and/or leukemia in both adults and children; and (*c*) identical schedules and routes of administration of the drugs were used in both populations.

Nonparametric methods were employed in the analyses of these data. The sign test (7) was utilized to compare paired adult and pediatric MTDs and recommended phase II doses. The median test (8) was used to compare the ratio of MTDs in children and adults between solid tumors and leukemia.

RESULTS

Eighteen drugs met the established criteria, 14 in solid tumor patients and eight in leukemia patients (table 1). The dose-limiting toxic effects observed are reported in table 2. Three drugs induced disparate toxic effects in the two populations. Cyclocytidine, a slow-release form of cytarabine resistant to deamination, produced severe postural hypotension in 50% of the adult patients at

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TABLE 1.—Drugs with phase I trials in adults and corresponding schedules in children

Drug	Year IND* filed	Tumor type
5-Azacitidine	1971	Leukemia
Teniposide	1972	Solid tumors
Cyclocytidine	1973	Solid tumors
Diglycoaldehyde	1973	Leukemia
Dianhydrogalactitol	1974	Solid tumors
Chlorozotocin	1976	Solid tumors
Zorubicin	1976	Leukemia + solid tumors
3-Deazauridine	1976	Leukemia + solid tumors
Amsacrine	1977	Leukemia
Indicine *N*-oxide	1977	Leukemia + solid tumors
Alanosine	1978	Solid tumors
ICRF-187	1978	Solid tumors
Diaziquone	1979	Leukemia + solid tumors
DON	1979	Solid tumors
Mitoxantrone	1979	Solid tumors
Bisantrene	1981	Solid tumors
Carboplatin	1981	Solid tumors
Anhydro-ara-F cytidine	Not NCI	Leukemia

* IND = investigational new drug application.

doses which were not consistently myelosuppressive. In children, doses up to 60% higher, while inducing prolonged myelosuppression, did not elicit this phenomenon. The mechanism of this hypotension (refractory to propanolol, ephedrine, and steroids) is unclear, although depletion of peripheral neurotransmitters and competitive blocking of vascular receptor sites for vasoconstrictor substances have been postulated (9). ICRF-187, a bifunctional alkylating agent, produced transient elevation of liver enzymes and prolonged prothrombin time and partial thromboplastin time in children at nonmyelosuppressive doses which were 2.8 times higher than those which induced severe myelosuppression in adults. Since no adult leukemia patients have been treated with ICRF-

TABLE 2.—Comparison of dose-limiting toxic effects of anticancer agents in children and adults

Drug	Schedule	Dose-limiting toxic effect	
		Children	Adults
Anhydro-ara-F cytidine	Daily × 5	Aplasia*	Aplasia*
Alanosine	Daily × 3	Mucositis	Mucositis
Amsacrine	Daily × 3	Stomatitis/nausea and vomiting*	Stomatitis/nausea and vomiting*
Bisantrene	Daily × 1	Myelosuppression	Myelosuppression
	Daily × 5	Myelosuppression	Myelosuppression and phlebitis
Chlorozotocin	Daily × 1	Myelosuppression	Myelosuppression
Diaziquone	Daily × 5	Myelosuppression; hepatotoxicity*	Myelosuppression; hepatotoxicity*
Dianhydrogalactitol	Daily × 5	Myelosuppression	Myelosuppression
Diglycoaldehyde	Daily × 5	Renal toxicity*	Renal toxicity*
DON	2 ×/wk	Myelosuppression; nausea and vomiting	Myelosuppression; nausea and vomiting
ICRF-187	Daily × 5	Hepatotoxicity	Myelosuppression
Indicine *N*-oxide	Daily × 5	Hepatotoxicity	Myelosuppression
Mitoxantrone	Daily × 1	Myelosuppression	Myelosuppression
Zorubicin	Daily × 1	Myelosuppression	Myelosuppression
Teniposide	Daily × 5	Myelosuppression	Myelosuppression
Cyclocytidine	Daily × 10 sc	Myelosuppression	Myelosuppression and hypotension
3-Deazauridine	Daily × 5	Myelosuppression	Myelosuppression
5-Azacitidine	Daily × 5	Nausea and vomiting	Nausea and vomiting

* Leukemia patients.

187, it is not known whether hepatotoxicity would surface in adult patients with leukemia given higher doses of ICRF-87. With indicine *N*-oxide, severe veno-occlusive disease was observed at nonmyelosuppressive doses in children (10); cases of veno-occlusive disease were also observed in adults, but only at higher doses (11).

Table 3 compares the MTD reached in children and adults with solid tumors, and shows the ratio between the childhood and adult doses. A ratio > 1 indicates that children tolerate more drug than adults, while a ratio < 1 means that the dose-limiting toxicity in children appeared at doses below the adult MTD. The MTD ratio varies widely, with a range of 0.66–2.8. Nonetheless, the median ratio is 1.3, and for five agents (35%), it is roughly 1.5. However, for two drugs, indicine *N*-oxide and diaziquone, the ratio is well below 1, suggesting that children are less tolerant of these agents than adults.

The MTD is the highest tolerable dose that can be achieved without producing irreversible toxicity. Because of the small number of patients treated in phase I trials, the MTD is merely an estimation of the optimal dose. Since our primary concern is the comparison of clinically employed doses, we calculated the ratio between phase II recommended doses for children and adults (table 3). While the distribution varies with a range that is identical to that for the MTD ratio, 0.66–2.8, the median is 1.5 with the difference between populations being statistically significant ($P = 0.002$). Only one drug, indicine *N*-oxide, has a ratio of < 1.

The MTD of eight drugs for adults and children with leukemia is reported in table 4. Three of the eight drugs show a ratio slightly > 1, and four have a ratio of < 1. The ratio for the phase II dose is equal to 1 for three drugs and < 1 for the remaining drugs. These differences are not statistically significant.

Figure 1 plots the ratios of childhood to adult doses for the drugs and schedules in table 3. These ratio comparisons are made separately for MTD and phase II doses in both solid tumor and leukemia trials. For recommended phase II doses, the leukemia dose ratios are lower than solid tumor ratios ($P = 0.004$). This suggests that while children with solid tumors appear to tolerate higher doses of drug than adults, this is not the case for patients with childhood leukemia.

In an attempt to understand the discrepancy in dose tolerance between adults and children, we analyzed patient characteristics which might be the basis for such differences. Since the end point was to assess differences between representative samples of the adult and childhood populations, all NCI phase I patient data since 1980 were pooled. Data from 277 children and 1921 adult patients were analyzed for the following characteristics: performance status, prior treatment, patient deaths on study, and response. In addition, pretreatment values for renal and hepatic functions were taken as an indirect

TABLE 3.—Comparison of MTD and recommended phase II dose in children and adults with lymphomas and solid tumors

Drug	Schedule	MTD (mg/m²)			Phase II dose (mg/m²)			Ref No.
		Children	Adults	Ratio*	Children	Adults	Ratio*	
ICRF-187	Daily × 3	3500	1250	2.80	3500	1250	2.80	23,24
Cyclocytidine	Daily × 10 sc	600	> 360	< 1.66	600	360	1.67	25,26
	Daily × 10 iv	600	450	1.33	Not recommended			9
3-Deazauridine	Daily × 5	2800	1800	1.55	2000	1200	1.66	27,28
Teniposide	Daily × 5	45	30	1.50	45	30	1.50	29,30
Mitoxantrone	Daily × 1	18	12	1.50	18	12	1.50	31,32
Carboplatin	Weekly × 4	210	150†	1.4	175	125	1.40	33,34
	Daily × 1	590	440–500	1.34–1.18	560	400	1.31	34–36
Bisantrene	Daily × 5	120	90	1.30	100	80	1.25	37,38
	Daily × 1	300‡	280	1.07	280‡	260	1.08	39
Dianhydrogalactitol	Daily × 5	50	40	1.20	50	30	1.70	40,41
DON	2 ×/wk	520§	500	1.10	520§	300	1.73	42
Chlorozotocin	Daily × 1	150	150–200	1.00/0.75	150	120–150	1.25/1.00	43–45
Zorubicin	Daily × 1	450¶	400	1.00	300¶	150	2.00	46,47
Alanosine	Daily × 3	350**	375	0.93	300**	250	1.20	48
Indicine *N*-oxide	Daily × 1	7500††	9000	0.83	7500††	7000	1.07	49,50
	Daily × 5	2000	3000‡‡	0.66	2000	3000	0.66	10,51
Diaziquone	Daily × 5	9	12	0.75	9	8	1.12	52–54

*Ratio = $\frac{\text{MTD, children}}{\text{MTD, adults}}$.

†Woolley P. Personal communiction.

‡Minutes of the Phase I Working Group meeting, Bethesda, MD, Jan 19–21, 1984.

§Sullivan M. Personal communication.

¶Ragab A. Personal communication.

**Cancer Therapy Evaluation Program Annual Report to the Food and Drug Administration. Alanosine, Apr 1984.

††Cancer Therapy Evaluation Program Annual Report to the Food and Drug Administration. Indicine *N*-oxide, June 1982.

‡‡No prior treatment; 2250 if prior nitrosoureas.

TABLE 4.—Comparison of MTD and recommended phase II dose in children and adults with acute leukemia

Drug	Schedule	MTD (mg/m²)			Phase II dose (mg/m²)			Ref No.
		Children	Adults	Ratio*	Children	Adults	Ratio*	
Anhydro-ara-F cytidine	Daily × 5	30†	20†	1.33	Not recommended			65,66
3-Deazauridine	Daily × 5	7200	6000	1.2	2000	3000	> 0.66	27,55
Diaziquone	Daily × 5	30	28	1.07	25	24	1.04	52,56
Zorubicin	Daily × 1	450	450	1.00	300	450	0.67	57,67
Indicine *N*-oxide	Daily × 5	2500	3000‡	0.83	2500	3000	0.83	10,11,58
Amsacrine	Daily × 5	150	200	0.75	120	120	1.00	59-61
Diglycoaldehyde	Daily × 5	1500	2000	0.75	1500	1500	1.00	62,63
5-Azacitidine	Daily × 5	300	400	0.75	150	300	0.50	56,64

*Ratio = $\frac{\text{MTD, children}}{\text{MTD, adults}}$.

†Mg/kg.

‡Original MTD at 3750; subsequent patient tolerated only 3000.

measure of possible organ dysfunction. Performance status distribution was very similar in the two populations, with at least 20% of the patients being grade 3 or 4. The populations differed with regard to exposure to prior treatment (100% of the children vs 75% of the adults, $P < 0.005$) and the percent of patients who died on study (21% of the children vs 15% of the adults, $P < 0.05$). Children were better responders than adults [7.5% of the children vs 1.7% of the adults (partial plus complete response)]. Both adult and childhood parameters for pretreatment renal (BUN and serum creatinine) and liver (total bilirubin, transaminase, and alkaline phosphatase) function were within normal limits. Thus, there were no major differences in patient characteristics which might have accounted for the observed differences in dose tolerance.

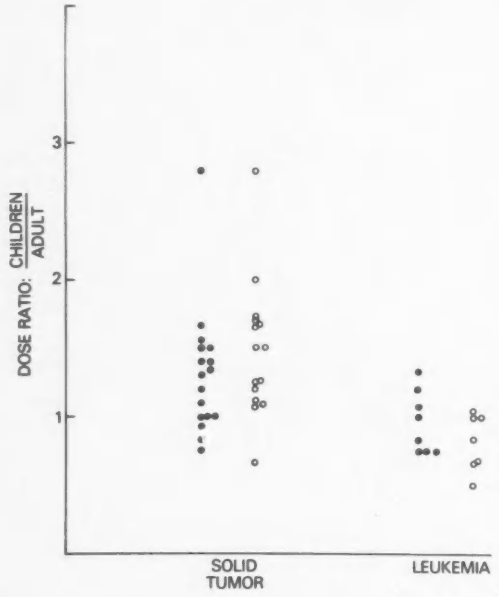

FIGURE 1.—Comparison of the children:adult ratios in solid tumors vs leukemia. ● = MTD ratios; ○ = phase II dose ratios.

DISCUSSION

This retrospective analysis of qualitative and quantitative toxic effects of antineoplastic agents in adults and children suggests that the two populations differ in their thresholds for developing toxicity. Children with solid tumors appear to have a greater dose tolerance than adults, while children with leukemia appear to have a tolerance equivalent to adults. Moreover, even among solid tumor patients, certain drugs produce exceptions to the rule of greater child tolerance. A multitude of factors, ranging from intrinsic age-related physiologic differences in drug metabolism to extent of prior treatment, may be responsible for this mosaic of clinical observations in children. The increased tolerance of children with solid tumors may simply be a reflection of increased bone marrow reserve associated with youth, as suggested by Glaubiger et al (6). The way phase I trials in children are currently conducted makes it very difficult to dissect the precise impact that each of the many factors has on drug tolerance.

Two particular factors that cloud interpretation of results in pediatric patients are the imprecision with which the upper age limit of the pediatric population is defined and the lack of recognition of specific age-related cohorts within the entire pediatric population. From a physiological point of view, children are not "little adults," but rather, immature individuals subject to a continuous state of development (4); marked variations exist in drug distribution and elimination via renal excretion or hepatic metabolism according to age (4,5). For instance, the relative volumes of the body water compartment,

total-body water, and extracellular water decrease progressively from infancy to adulthood (12). This would lead one to predict a greater tolerance in children, and, in fact, a larger volume of distribution in children was documented for ICRF-187, the compound with the highest children/adult toxicity ratio (13). Greater rates of plasma elimination in children than adults have also been reported for cyclophosphamide (14), methotrexate (15), and etoposide (16). The overall rate of hepatic metabolism also decreases from late infancy through childhood to adolescence and adulthood (17). This factor may have played a role in the increased toxicity observed with indicine *N*-oxide in younger, smaller children where hepatic metabolism is thought to be responsible for the production of the toxic metabolite dehydroindicine.[4,5]

Dosing may be another important factor contributing to the difference in tolerance in children as compared to adults. Although dosage on a surface area basis, as currently used, may be more valid than on a body weight basis because of its correlation with physiologic functions, this method is still inadequate to allow for the large variability in size among infants, toddlers, and children. A recently published paper suggested the reintroduction of the milligram per kilogram dosage in children < 1 m^2 following the observation of life-threatening neurotoxicity with a standard vincristine dose of 1.5 mg/m^2 in small children with acute lymphoblastic leukemia (18). Preliminary analysis of the experience with indicine *N*-oxide at higher doses suggests that a similar effect may account for the more severe toxicity observed in children.[5]

In this analysis, dose-limiting toxicity differed in adults and children in three of the 18 drugs considered. The mechanism underlying this phenomenon has not been delineated; dose tolerance appears to be the likely explanation for indicine *N*-oxide and perhaps ICRF-187, although not for cyclocytidine. Marked differences in toxicity were noted during clinical trials of two other compounds, procarbazine and azapicyl, but these were not included in this analysis due to the lack of corresponding schedules in adults and children. With both compounds, seizure and neuropathy were seen in adult patients but not in children (19–22).

These data underscore the need for independent phase I trials tailored for children. For adults, the investigational drug starting dose is calculated from mouse lethality studies, and the modified Fibonacci schema is used for escalating doses (23). A minimum of three patients with no previous exposure to the drug under evaluation are entered at each escalation step and at least six patients are entered at the recommended phase II dose in order to minimize the risk of under- or over-dosing in subsequent trials. Separate phase I trials are conducted in leukemia, and these are usually initiated after a myelosuppressive dose has been established in solid tumor patients.

A similar approach has been used in children, the starting dose for phase I trials being based on some fraction of the adult MTD, with escalation according to Fibonacci. Prior to 1980, the starting doses in children, when calculated as a percent of the adult MTD, varied widely, from 1% to 80%. The number of escalations required to reach the MTD also varied enormously. Following an initial review of this experience (6), the NCI recommended that phase I trials in children commence at 80% of the adult MTD, as the minimum childhood MTD was found to be 83% of its adult counterpart. Escalation procedures, however, were unspecified.

The current analysis allows us to redefine the approach for choosing starting doses and escalation procedures for phase I trials in children. Basing the childhood starting dose on the adult experience should minimize the entry of patients at a biologically inactive dose, thus increasing the probability of response, without placing the patients at undue risk of toxicity. Escalation procedures that employ the fewest dose levels between entry and MTD, yet do not escalate into an area of overt toxicity, are preferred. Both these maneuvers aim at reducing the number of patients required to estimate the proper dose for subsequent efficacy trials.

Scrutiny of tables 3 and 4 confirms that phase I trials in patients with solid tumors and leukemia should be approached separately. The overwhelming majority of solid tumor trials in children arrived at the MTD above those of adults, while this was less often seen in children with leukemia. The data support continuing the entry of children with solid tumors and leukemia at a dose approximately 80% of the adult solid tumor MTD. With the exception of indicine *N*-oxide on one of the two schedules tested, no drug would have required de-escalation to avoid toxicity. In the absence of nonhematologic toxicity, leukemia patients would then be escalated directly from the childhood MTD for solid tumor patients rather than from adult leukemia doses, since the adult leukemia phase II doses are generally higher than their pediatric counterparts (table 4). In the event that the drug has not been evaluated in children with solid tumors, the starting dose for children with leukemia should be $< 75\%$ of the adult leukemia MTD.

Escalation from the starting dose should not follow the conventional Fibonacci schema, since the risk of escalating into an area of overt toxicity increases proportionally along the dose-toxicity curve. Figure 2 depicts the outcome of phase I trials with drugs discussed in this paper if the starting dose in children had been 80% of the adult MTD, and a fixed 33% increment (as employed by the later steps of the Fibonacci schema) had been used in each subsequent dose escalation level. With the exception of ICRF-187, from one to three escalations would have been required to reach the MTD. This efficacy, however, is off-

[4]Ames M. Personal communication.
[5]Miser J. Personal communication.

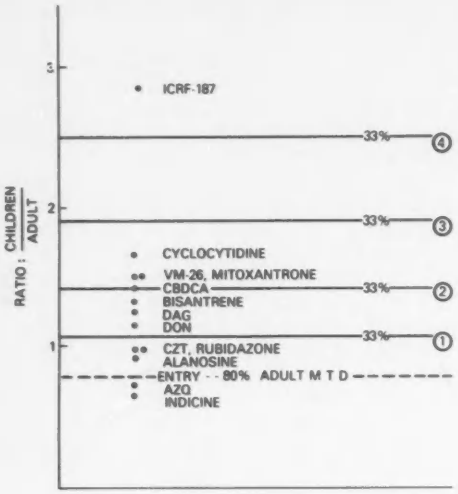

FIGURE 2.—Experimental MTDs in children expressed as a function of children:adult ratios for 11 antineoplastic drugs. Nos. on the right represent dose levels based on 33% increments. Symbols for the indicated drugs reflect the No. of escalations required to reach the MTD if the starting dose had been 80% of the adult MTD (*see* text for discussion). VM-26 = teniposide; CBDCA = carboplatin; DAG = dianhydrogalactitol; CZT = chlorozotocin; rubidazone = zorubicin; AZQ = diaziquone; and indicine = indicine *N*-oxide.

set by the increased likelihood of escalating to a dose which produces unacceptable toxicity. It should be remembered that the entry doses for these childhood trials are intended to approximate those that produced overt toxicity in adults, and the margin of safety is accordingly reduced. Escalations at a fixed increment of 20% (starting at 80% of the adult MTD and proceeding through 96%, 115%, 138%, 156%, etc) retain much of the efficiency yet reduce the likelihood of overshoot.

In summary, the NCI is currently recommending that phase I trials in children: (*a*) begin in patients with solid tumors and leukemia at 80% of the MTD in adults with solid tumors: (*b*) be designed so that patients with solid tumors and leukemia are entered at each level; and (*c*) be escalated at fixed 20% increments, distinguishing between the toxic effects observed in patients with leukemias (for whom myelosuppression is a sought-after effect) and patients with solid tumors, and in the absence of nonmyelosuppressive toxicity, escalating in patients with leukemia beyond the solid tumor MTD.

It should be recognized, however, that these recommendations are not rigid. There may be instances in which arguments may be made for testing specific new agents in children without prior testing in adults; nevertheless, given the scarcity of subjects eligible for childhood phase I trials, every effort should be made to base these trials on data obtained in adults.

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Phase II Study of Low-Dose Mitomycin in Patients With Ovarian Cancer Previously Treated With Chemotherapy[1,2]

Richard H. Creech,[3,4,*] Mukund K. Shah,[3] Robert B. Catalano,[3,5] Kathleen Dierks,[3] Hari Dayal,[3,6] and Robert Goldberg-Alberts[3]

Forty-three evaluable patients with ovarian cancer who had failed one or more chemotherapy regimens were treated with mitomycin iv at 28-day intervals. Thirty-six patients with good bone marrow reserve received 10 mg/m² and seven patients with poor bone marrow reserve received 6.7 mg/m² initially. Ten patients (23%) responded. Patients with an Eastern Cooperative Oncology Group performance status of 0–1 had better response rates and survivals as compared to patients with a performance status of 2–4 (44% vs 8%; median survival, 8 vs 4 months). The acute hematologic and gastrointestinal toxicity was minimal. No patients developed pulmonary, renal, cardiovascular, or local tissue toxicity. [Cancer Treat Rep 69:1271–1273, 1985]

Mitomycin, used at half-standard doses (10 mg/m²) at 4-week intervals, has been found to have antineoplastic effect in hormone- and chemotherapy-refractory patients with metastatic breast cancer and to be associated with minimal toxicity (1). To determine whether this drug regimen is also active in advanced ovarian cancer, a phase II study was conducted in patients with advanced ovarian cancer who had previously failed one or more chemotherapy regimens.

PATIENTS AND METHODS

Patient eligibility requirements included: pathologic proof of ovarian cancer, progressive disease after one or more therapeutic regimens, measurable or clearly evaluable malignant disease, wbc count $\geq 4000/mm^3$, platelet count $\geq 100{,}000/mm^3$, and BUN ≤ 20 mg/dl.

After giving informed written consent, patients without previous pelvic irradiation or prolonged chemotherapy-induced cytopenias (good bone marrow reserve) were given mitomycin iv at a dose of 10 mg/m² at 28-day intervals until evidence of malignant disease progression was noted. Patients with a known poor bone marrow reserve or platelet counts of 100,000–120,000/mm³ on the scheduled day of mitomycin administration received 6.7 mg/m². If platelet counts were $< 100{,}000/mm^3$, platelet counts were repeated at weekly intervals until the platelet count was $\geq 100{,}000/mm^3$. At that time, the mitomycin was given at 2.3 mg/m². In patients who had platelet counts $< 100{,}000/mm^3$ after 2.3-mg/m² doses, the intervals were lengthened in order to maintain platelet counts at $\geq 100{,}000/mm^3$ on the day of mitomycin administration.

Before entry into this study, each patient underwent an evaluation of end-organ function and disease extent. Included were a hematocrit, wbc count, platelet count, a chemistry profile, chest roentgenogram, ECG, and a physical examination including pelvic and rectal evaluations. All clinically evident metastatic disease was measured or evaluated, and was then documented. A hematocrit, wbc count, platelet count, and all parameters of malignant disease were recorded prior to each administration of mitomycin. Chemical profiles were

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obtained at 3-month intervals. Other studies were performed when indicated clinically.

Eastern Cooperative Oncology Group (ECOG) (2) criteria for response and toxicity were used. The partial response (PR) rates were determined, and the time to response and duration of response were combined to give the time to progression. By analyzing the time to progression of the responding and stable patients, a comparison of the durations of mitomycin effect could be made. Probability curves were compared using the method of Mantel-Haenszel (3).

RESULTS

Of the 50 patients entered on this study, 43 were evaluable for toxicity and response evaluations. Three patients died of progressive malignant disease within 30 days of mitomycin initiation; three did not return for the second course of therapy; and one did not receive the correct mitomycin dose.

The characteristics of the 43 evaluable patients are summarized in table 1. It can be seen that many of the patients studied were not optimal candidates for a phase II drug trial because of poor performance status (PS), extensive previous chemotherapy, or poor response to previous chemotherapy regimens.

TABLE 1.—Characteristics of 43 evaluable patients

Characteristics	No. of patients
Median age in yrs (range): 58 (25–81)	
Median interval from diagnosis to mitomycin in mos (range): 9 (2–76)	
ECOG performance status	
0	1
1	17
2	11
3	10
4	4
Pathologic classification	
Papillary serous cystadenocarcinoma	27
Poorly differentiated adenocarcinoma	8
Mucinous cystadenocarcinoma	4
Endometrioid adenocarcinoma	2
Clear cell carcinoma	1
Granulosa cell carcinoma	1
Stage at diagnosis	
I	3
II	5
III	28
IV	7
Types of previous therapy	
Pelvic irradiation	5
Alkylator	29
Doxorubicin-containing regimens	10
Cisplatin-containing regimens	1
Doxorubicin- and cisplatin-containing regimens	7
Other	13
No. of previous treatment regimens	
1	24
2	15
3	3
4	1

In table 2, the response rates, median times to progression, and median survival times (in months) are shown. The responders and patients with stable disease had median tim s to progression of 4 months. The median survival times for the responders, patients with stable disease, and patients with progressive disease were 11, 8, and 3 months, respectively.

The PR rate of ten of 43 patients (23%) demonstrates that mitomycin, as administered, has anti-ovarian cancer activity. Nine of 36 patients with good bone marrow reserve and one of seven patients with poor bone marrow reserve responded. Three of the ten patients responding to mitomycin had each previously responded to different regimens (melphalan, 5-FU-doxorubicin-cyclophosphamide, and cyclophosphamide-hexamethylmelamine-doxorubicin-cisplatin). None of the six patients with stable disease had had an earlier chemotherapy response. Of the 27 patients who had disease progression while receiving mitomycin, four had previously responded to doxorubicin-containing regimens and one had responded to cyclophosphamide-doxorubicin-cisplatin. None of the five patients treated with pelvic irradiation responded to subsequent chemotherapy regimens, including mitomycin.

When evaluating organ site responses, pelvic and abdominal masses were most responsive (eight PR in 23 patients, two PR in 13). Subcutaneous masses (one PR in two patients), ascites (one PR in 16 patients), pleural effusions (one PR in two patients), and groin nodes (one PR in one patient) were also responsive. There were no responses in the liver in four patients and no responses in supraclavicular nodes in four patients.

Eight of 18 patients with an ECOG PS of 0–1 had PR (44%), while only two of 25 patients with a PS of 2–4 had PR (8%). The difference in survival time between the patients with a PS of 0–1 (median, 8 months) and a PS of 2–4 (median, 4 months) approaches significance ($P = 0.06$).

By using this one-half mitomycin dose regimen and the dosage modification schema for good or poor bone marrow reserve and thrombocytopenia, the toxicity

TABLE 2.—Responses, median times to progression, and median survival times

	No. of patients (%)	Median TTP (mos)*	Median survival (mos)
Responses			
PR	10 (23)	4	11
Stable	7 (16)	4	8
Disease progression	26 (61)	—	3

*TTP = times to progression.

was modest. Of the 43 evaluable patients, four required transfusions for anemia, seven had a wbc count of 2000-2900/mm^3, none had a wbc count < 2000/mm^3, 16 had vomiting, and one each had mild diarrhea or mouth ulcers. No patient had renal, pulmonary, cardiovascular, or local tissue damage during the 273 courses of mitomycin administered. The percent of patients receiving 10 mg/m^2 of mitomycin decreased with each course of therapy (Course 1, 84%; Course 2, 61%; Course 3, 35%; Course 4, 30%; Course 5, 17%; and Courses 6-8, 0%). No patient had serious chronic toxicity from this therapy.

DISCUSSION

Alkylating agents including melphalan, cyclophosphamide, triethylene-thiophosphoramide, and chlorambucil, as well as nonalkylating agents methotrexate, 5-FU, vincristine, progestins, doxorubicin, hexamethylmelamine, and cisplatin, have been found to be active singly or in combination against ovarian cancer. As primary therapy, melphalan has half the response rate and duration of cisplatin-containing regimens, but no survival disadvantage. Subsequent chemotherapy after initial chemotherapy failure has resulted in low response rates and short-lived response durations. The purpose of this study was to determine if iv mitomycin has an anti-ovarian cancer effect. It is known to have a maximum urinary excretion of 15%, enterohepatic circulation, and penetration into ascites (4,5). In a review of the mitomycin literature, Crooke and Bradner (6) found six objective responses to mitomycin in 27 patients treated by multiple investigators.

In this study of 43 patients with previously treated ovarian cancer, mitomycin was found to have antineoplastic effect with a 23% PR rate. The median time to progression of the patients with PR and stable disease was 4 months. The median survival times of the patients with response, stable disease, and progressive disease were 11, 8, and 3 months, respectively. Pelvic and abdominal masses were the most responsive organ sites. Performance status significantly influenced the response rates and survival, with the patients with a PS of 0-1 having a 44% PR rate (median survival, 8 months) compared to an 8% PR rate (median survival, 4 months) for the patients with a PS of 2-4.

Although the acute hematologic and gastrointestinal toxic effects in these patients with ovarian cancer are similar to those in patients with metastatic breast cancer who have been treated with the same regimen (1), the lack of perivenous and cardiac toxicity in this study is most likely related to a shorter duration of previous chemotherapy, a decreased previous exposure to doxorubicin, and fewer courses of mitomycin administered per patient. In this study, as in the breast cancer study, titration of mitomycin dose by utilizing an algorithm based on platelet count on the day of scheduled therapy permits chronic intermittent mitomycin administration without prolonged cessation of therapy due to thrombocytopenia.

This study demonstrates antineoplastic activity of mitomycin at one-half the standard dose in patients with advanced ovarian cancer after previous chemotherapy failure. Combination of this chemotherapeutic regimen with other active drugs such as cisplatin and hexamethylmelamine should be considered for study as a first-line combination regimen for ovarian cancer.

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Phase II Trial of Epirubicin in Gastric Cancer[1]

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Patients with advanced inoperable or recurrent adenocarcinoma of the stomach received an iv bolus of epirubicin (75 mg/m^2) every 3 weeks. Partial responses were observed in four of 24 evaluable patients (17%). Treatment was generally well tolerated; a drop in left ventricular ejection fraction was observed in one patient who had received 450 mg/m^2 of epirubicin. [Cancer Treat Rep 69:1275–1277, 1985]

Doxorubicin has been shown to be an active agent in the treatment of advanced stomach cancer, with a response rate of 22%–24% in previously untreated patients (1–3). These responses are, however, short-lived, lasting only 4–6 months. When doxorubicin is used in combination chemotherapy, response rates ranging from 30% to 63% are observed (4). Epirubicin differs from the parent compound by epimerization of the hydroxyl group at the 4 position. Phase I and II studies of epirubicin in man have demonstrated activity in a range of tumors, with a pattern of acute toxicity similar to doxorubicin but quantitatively less. In particular, it is claimed that the incidence of cardiotoxicity in patients receiving epirubicin is lower than in patients receiving doxorubicin (5,6). In view of these reports that epirubicin showed significantly less toxicity, it was proposed to evaluate the efficacy and toxicity of epirubicin in the treatment of patients with advanced gastric cancer.

MATERIALS AND METHODS

All patients had symptomatic histologically proven advanced adenocarcinoma of the stomach. Two patients had received interferon therapy, but no patients had received previous chemotherapy or radiotherapy. A normal blood count, Karnofsky performance status of > 50%, and no evidence of cardiac disease were criteria for entry into the study. All patients had objective evidence of disease by clinical bidimensional measurement, computerized tomography, or ultrasound scanning. Informed consent was obtained prior to beginning treatment.

An iv bolus injection of epirubicin (75 mg/m^2) was administered every 3 weeks. The patients were fully evaluated after three courses. All patients whose disease had shown a response or no change were to continue on therapy for a maximum of 12 cycles. Patients with evidence of progression of their malignancy were withdrawn from the study. Partial response was defined as a 50% reduction in the product of the two largest perpendicular diameters, lasting for at least 4 weeks. No change was defined as a decrease of < 50% or an increase of < 25% in the product of the two largest perpendicular diameters. Disease progression was considered to have occurred when the product of the two largest perpendicular diameters increased by > 25%.

Acute toxicity was assessed using World Health Organization criteria (7). In addition, to evaluate cardiotoxicity in more detail, left ventricular ejection fraction was measured using the gated equilibrium blood pool method (8). To provide a baseline, the ejection fraction was measured on two occasions at the beginning of treatment. Studies were repeated after the third and subsequent courses of treatment in patients who continued therapy.

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Sex	
Males	19
Females	5
Median age in yrs (range)	52 (33-75)
Median Karnofsky performance status (range)	60% (50%-90%)
Inoperable primary	20
Recurrent tumor	4
Prior treatment	
Interferon	2
Chemotherapy	0
Median time from diagnosis to chemotherapy in wks (range)	3 (1-8)
Median duration of symptoms to chemotherapy in wks (range)	12 (4-52)
Method of tumor assessment	
Computerized tomographic scan	12
Palpation	11
Ultrasound scan	1

TABLE 2.—Cumulative dose of epirubicin administered

Total dose received (mg/m^2)	No. of patients
75	3
150	2
225	7
300	3
375	4
450	3
525	1
675	1

RESULTS

Between October 1981 and June 1983, 26 consecutive patients with advanced gastric adenocarcinoma were entered into the study. One patient died before chemotherapy was started, and one patient was not considered evaluable because ascites was the only measurable evidence of disease. Characteristics of the 24 evaluable patients are shown in table 1. All other patients, even if they received only one injection of epirubicin, were considered eligible for response and toxicity evaluation. The cumulative dose of epirubicin administered is shown in table 2. Partial responses were observed in four of the 24 evaluable patients (17%). Three partial responses were observed in patients with lymph node masses, and a fourth was observed in a patient with liver metastases. The partial responses were of short duration (4, 9, 12, and 20 weeks). The survival for partial responders from the beginning of chemotherapy was 10, 17, 24, and 32 weeks; overall median survival of the 24 evaluable patients was 10 weeks.

In general, the acute toxicity was mild (table 3). The anemia observed in seven patients was considered to be predominantly due to bleeding from the primary tumor.

Left ventricular ejection fractions were estimated in 16 patients prior to starting chemotherapy. Eight patients had the studies repeated after three courses; five had estimations after four or five courses; and two had estimations after six courses of epirubicin. A significant drop in the left ventricular ejection fraction was seen in one patient, in whom the left ventricular ejection fraction fell from a baseline of 65% to 54% after four courses and showed another fall to 43% after the sixth course of treatment. This fall in ejection fraction was associated with early clinical signs of left ventricular failure, of which the patient was not symptomatic. At this time, the patient's disease was showing progression, so therapy was stopped and he died of advancing disease 4 weeks later. Unfortunately, a postmortem examination was not performed.

DISCUSSION

In this phase II study, four of the 24 evaluable patients obtained partial response. The response rate was 17%, with 95% confidence limits of the true response rate being between 5% and 37%. Kolaric et al (5) have reported two complete and two partial responses in 15 patients with gastric cancer, giving a response rate of 27%. In his review, Ganzina (9) found four partial responses (24%) in 17 patients with gastric cancers pooled from seven different phase II studies. Therefore, in all available data, including the present study, there have been 12 responses (21%) in 56 patients with gastric cancer who have received treatment with epirubicin. The response rate to epirubicin appears to be very similar to that reported for doxorubicin (22%-24%).

The dose of epirubicin used in this study (75 mg/m^2 every 3 weeks) was well tolerated and the toxicity observed was similar to previous phase I and II studies reviewed by Ganzina (9). The lack of myelotoxicity observed in this trial indicates that larger doses of epirubi-

TABLE 3.—Acute treatment toxicity*

Toxic effects	Grade†				
	0	1	2	3	4
Nausea and vomiting	3	14	7	—	—
Mucositis	21	2	1	—	—
Diarrhea	21	3	—	—	—
Alopecia‡	4	9	7	4	—
Cardiotoxicity	23	0	1	0	—
Renal	24	—	—	—	—
Hemoglobin§	17	6	1	—	—
Wbc count§	22	1	1	—	—
Platelet count§	24	—	—	—	—

* Values = No. of patients.
†Grades are according to World Health Organization criteria (ref 7).
‡6 patients, 4 with grade 0 and 2 with grade 1, received scalp cooling.
§Evaluation 3 wks after administration of epirubicin.

cin could be safely used in future studies. The dose of epirubicin administered in other studies has varied from 75 to 90 mg/m^2 by iv bolus injection every 3 weeks, with the exception of Kolaric et al (5), who adopted a regimen of 40–50 mg/m^2 iv on 2 consecutive days every 3 weeks. The cumulative dose of epirubicin administered was relatively small in most patients; only two patients received > 500 mg/m^2 (525 and 675 mg/m^2).

A significant drop in left ventricular ejection fraction was demonstrated in a patient who had received 450 mg/m^2 of epirubicin. Left ventricular ejection fractions obtained from the gated equilibrium blood pool method are only a moderately sensitive screen for detecting anthracycline cardiotoxicity. Increased sensitivity could have been obtained by measuring ejection fraction while exercising, as well as at rest, or by the use of endomyocardial biopsy. The poor performance status of this group of patients made these more sensitive tests impossible. Ganzina (9), in his review of 700 patients, described two patients suffering from congestive cardiac failure, which was classified as mild to moderate and reversible. The cumulative doses of epirubicin in those patients were 1120 and 1235 mg/m^2.

The response rate to epirubicin in patients suffering from gastric cancer has been low and the responses obtained have been short. However, the response rate is similar to that obtained with doxorubicin used as a single agent. In view of the similar activity but reduced toxicity of epirubicin, further evaluation of this agent in combination chemotherapy is indicated.

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Pharmacokinetic Evaluation of Increasing Dosages of Etoposide in a Chronic Hemodialysis Patient[1]

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A chronic hemodialysis patient was treated for small cell lung cancer with a combination therapy consisting of doxorubicin, cyclophosphamide, and etoposide. The dose of etoposide was increased to normal in five steps because of the possible accumulation and higher plasma peak levels due to terminal renal failure. In order to study this phenomenon, plasma, urine, and dialysate levels of etoposide were determined during five treatment courses with a high-performance liquid chromatographic method combined with electrochemical detection; this proved that the pharmacokinetic curves for etoposide fit a two-compartment model. Peak plasma levels were 7.96, 10.84, 18.24, 21.0, and 24.0 μg/ml for dosages of etoposide of 75, 100, 150, 200, and 250 mg, respectively. No accumulation occurred, half-life times of the elimination phase were between 8.7 and 23.0 hours, apparent distribution volumes of the central compartment were between 9.2 and 14.5 L, and the total-body clearances were between 2.1 and 2.8 L/hour. Thus, pharmacokinetic parameters were comparable with those obtained in patients with normal renal function. Hemodialysis did not disturb the exponential decay of plasma etoposide concentration during the elimination phase. No etoposide was found in the dialysate and only minimal etoposide was recovered from the urine. The data presented here indicate that renal clearance is not indispensable for eliminating etoposide.
[Cancer Treat Rep 69:1279–1282, 1985]

A combination therapy of cyclophosphamide, doxorubicin, and etoposide was chosen for the treatment of anaplastic bronchial carcinoma in a chronic hemodialysis patient. From literature, it is known that after bolus injection or infusion of etoposide, the plasma concentration decreases by a bi-exponential decay (1-3). Within 72 hours after administration, the urinary recovery was 29% of the dose as unchanged drug and 14% of the dose as metabolite(s) (3). This indicates that both metabolism and renal excretion are important for the elimination of this drug. For this reason, it could be possible that normal dosages of etoposide administered to patients with decreased or absent renal function cause accumulation of etoposide and an increased toxicity.

For doxorubicin and cyclophosphamide, it is known that no dose adjustments are necessary in cancer patients with renal failure (4-6). Because of the unknown effect of the renal failure on the toxicity and pharmacokinetics of etoposide, an escalating dosage regimen for etoposide was followed.

METHODS

Case Report

The patient was a 60 year-old-man who was treated by chronic hemodialysis because of renal failure due to polycystic kidney disease (creatinine clearance < 5 ml/min). Biochemical parameters, including liver enzymes, bilirubin, alkaline phosphatase, and serum ferritin were all normal. The plasma albumin concentration during the five courses was constant (3.93 g/100 ml). The patient was dialyzed three times a week for 4 hours with a single needle double-headed pump system. A plate dialyzer with a Cuprophane membrane was used (Gambro Lundia Maior, Lund, Sweden). This membrane is 11 μM thick and

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has an effective surface area of 1.35 m^2. Approximate blood flow was 300 ml/min and dialysate flow was 500 ml/min.

After informed consent, the patient received etoposide in combination with doxorubicin and cyclophosphamide. Etoposide was given in a short infusion (15-60 mins) 2 hours after a hemodialysis session (ie, 42 hours before the next dialysis). Doxorubicin and cyclophosphamide were administered by bolus injection 3 minutes before etoposide administration. The administration of the drugs took place via the vascular access used for hemodialysis (ie, the arteriovenous fistula in the left forearm). The following dosages (mg/m^2) of etoposide, cyclophosphamide, and doxorubicin, respectively, were administered: *first course*—38, 508, and 31; *second course*—51, 964, and 41; *third course*—76, 609, and 31; *fourth course*—102, 609, and 31; and *fifth course*—127, 609, and 31.

In contrast to the ordinary dialysis sessions with a single pass of dialysate, a closed circuit system was used during the dialysis following the administration of cytostatic drugs to evaluate the dialyzability of etoposide. Ten liters of dialysate were used, which were replaced hourly, so that the total volume of dialysate was 40 L.

MATERIALS

Etoposide (Vepesid) and teniposide were obtained from Bristol-Myers Company. All other chemicals were of analytical reagent grade and were obtained from commercial sources. Solvents were used without further purification.

Sampling analysis.—Venous blood was sampled by an indwelling catheter with an occluding mandrel, which was placed in the left arm. The blood sampling scheme was: 0, 0.25, 0.5, 0.75, 1.25, 1.75, 2.25, 3.25, 6, 9, 12, 16, 22, and 40 hours after administration and every 30 minutes during the hemodialysis (42-46 hours after the administration). The heparin blood samples were separated by centrifugation (2000 × *g*) during 15 minutes; the plasma layer was stored at −20°C until analysis. Twenty-four hour urine collections were obtained for 3 days after drug administration. A sample was taken from each of the four containers with 10 L of dialysate, which had been used for 1 hour during the dialysis following drug administration. All samples were stored at −20°C until analysis. Etoposide was determined in plasma, urine, and the dialysate by high-performance liquid chromatography combined with electrochemical detection, as described previously (7).

Pharmacokinetic data analysis.—The plasma concentration time curves were presented on a semilogarithmic scale. Approximations of the pharmacokinetic parameters were determined by a least-squares regression analysis after curve stripping (8). These approximations functioned as starting values for a nonlinear least-squares regression analysis on a Control Data Cyber 175-180 computer. The reciprocal of the plasma concentration was used as a weighing factor. The calculated pharmacokinetic parameters from the fitting program are the distribution rate constant (α), the elimination rate constant (β), the first-order intercompartmental transfer rate constants (k_{12}, k_{21}), and the distribution volume of the central compartment (V_c). The volume of the distribution of the steady state (V_{ss}), elimination rate constant (k_e), and the total-body clearance (Cl_{tot}) was calculated as described by Gibaldi and Perrier (8).

RESULTS

Peak plasma concentrations increased from 7.96 to 24.04 μg/ml as the dose of etoposide increased. The curves showed a bi-exponential decline, indicating that the disposition of etoposide can be described by an open two-compartment model. The area under the curve (AUC) was linear with the administered dose ($r = 0.99$). The plasma concentrations measured during and after the hemodialysis following drug administration did not differ from the calculated elimination phase. Table 1 shows the pharmacokinetic parameters. Excretion of the unchanged etoposide in the urine over a period of 60 hours was measured after administration of 250 mg of etoposide; the cumulative urinary recovery was 1.2% of the dose. No etoposide was detected in the cumulative dialysate.

DISCUSSION

An escalating dose regimen for etoposide was used in this patient because of the unknown effect of the renal failure on the etoposide plasma levels and the toxicity. It was expected that dose adjustments would be necessary, since etoposide is partly eliminated by the kidneys (9,10).[5]

At the second treatment course, the dose of doxorubicin and cyclophosphamide was increased, which resulted in fever and severe leukopenia for 5 days (the wbc count dropped from 7.4×10^9/L to 0.8×10^9/L; simultaneously, the number of thrombocytes decreased from 200 to 70×10^9/L). For this reason, the dose of doxorubicin and cyclophosphamide was lowered at the third course. (During the other courses, only a small drop in the wbc and thrombocyte counts was observed without clinical effect.) Impotence was the only adverse clinical reaction which had already appeared after the first course. Adverse reactions were probably caused by cyclophosphamide and doxorubicin, since etoposide causes minor adverse reactions at this dose level. In treating cancer patients with severe renal failure, dose adjustments for doxorubicin were not recommended, and only minimal dose adjustments were made for cyclophosphamide (5).

[5]Holthuis JJM, Postmus PE, van Oort WJ, et al. Pharmacokinetics of high dose etoposide. Submitted for publication.

TABLE 1.—Pharmacokinetic parameters

D (mg/m^2)	$t_{1/2\alpha}$ (hr^{-1})	$t_{1/2\beta}$ (hr^{-1})	V_c (L)	V_{ss}* (L)	Cl_{tot}† (L/hr)	Cl_{tot}§ (L/hr)	AUC_∞¶ (mg·hr/L)	k_e (hr^{-1})
38	1.46	10.62	10.10	21.68	2.84	2.86	26.4	0.283
51	1.16	9.08	9.34	21.58	2.48	2.50	40.3	0.268
76	0.99	9.20	9.17	21.78	2.15	2.16	69.9	0.236
102	1.20	8.73	10.11	20.53	2.13	2.13	94.0	0.210
127	3.05	23.00	14.49	33.77	2.18	2.17	114.5	0.150
205–430 mg**	—	—	7.71	18.41	2.83	2.83	—	0.319
SD	—	—	2.79	5.57	1.31	1.83	—	0.096

* $V_{ss} = \frac{D \cdot AUMC_\infty}{(AUC_\infty)^2} - \frac{D \cdot T}{2 \cdot AUC_\infty}$

$AUMC_\infty = \frac{C_1}{\alpha^2} + \frac{C_2}{\beta^2}$

† $Cl_{tot} = \frac{D}{AUC_\infty}$

§ $Cl_{tot} = V_c \cdot k_e$

¶ $AUC_\infty = \frac{C_1}{\alpha} + \frac{C_2}{\beta}$

T = infusion time

**See ref 1.

Nevertheless, the doses were reduced as a precaution.

The linearity between etoposide dose and AUC_∞ indicates the absence of saturations of the metabolic enzyme system, and the noncompensated saturation of plasma proteins or saturated tissue binding up to a dosage of 127 mg/m^2. The pharmacokinetics were fitted according to a two-compartment open model. The fact that the model-independent total-body clearance (D/AUC_∞) is equal to the total-body clearance ($V_c \times k_e$) is an additional indication for the predicted model.

The found pharmacokinetics do not differ significantly from those obtained from a patient with normal renal functions (table 1). Except for the distribution volume of steady state (V_{ss}), all other pharmacokinetic parameters were normal. At the fifth course, the V_{ss} and the $t_{1/2\beta}$ increased significantly. The increase was possibly caused by the saturation of the plasma proteins responsible for etoposide binding, which results in an increase of the unbound fraction etoposide in plasma that is rapidly distributed through the body and leads to an increase of the V_{ss}. The elimination phase calculated during and after the hemodialysis did not differ significantly from the elimination phase before the hemodialysis.

The clearance of molecules of 588 daltons by hemodialysis is about 50–100 ml/min for the unbound fraction in the plasma (information from the manufacturer of Gambro Lundia Maior). The concentration of etoposide per milliliter of plasma just before the dialysis lies in the range of 100–400 ng/ml. Assuming an unbound fraction of 6% (in vitro) (1), then 70–600 ng/ml of etoposide is dialyzed in 4 hours. The concentration in the dialysate should be 2–15 ng/ml. Because of this, and the fact that no etoposide could be detected in the dialysate with the very sensitive high-performance liquid chromatography method, and also since the elimination phase showed no deviation from the elimination phase before hemodialysis, it can be concluded that etoposide is not dialyzed or adsorbed on the dialysis membrane. The fact that no etoposide is dialyzed is possibly due to the higher extent of plasma protein binding in vivo, which proved to be 98.4%[5] based on saliva concentration measurements as compared with in vitro experiments (1).

CONCLUSIONS

Etoposide administered to a patient with renal failure exhibited linear pharmacokinetics up to a dose of 127 mg/m^2, which might indicate that dose adjustments are not necessary for etoposide up to 127 mg/m^2 in these patients. More information on the pharmacokinetics of etoposide, especially given at higher doses, is necessary in patients with renal failure. Etoposide is usually not

dialyzed, or is dialyzed in very low amounts.

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Enhancement of Tumorigenicity of B16 Melanoma in Heterogenetic Mice by Administration of Copper Chelates[1]

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Exogenous copper was found to enhance tumorigenicity of B16 melanoma in heterogenetic mice that were treated with either the cupric chelate of nitrilotriacetic acid (NTA-Cu^{+2}) or the cuprous chelate of neocuproine (NC-Cu^{+1}). Both copper chelates were nontoxic to host mice given in the treatment schedule used here. Transplanted B16 melanoma cells were rejected after ip inoculation into CDF_1 mice unless they were pretreated with copper chelates, which permitted 100% tumor takes. A limited number of tumor takes were observed in untreated NIH Swiss mice, and treatment with copper chelates doubled the number of ip tumor takes. Treatment with NC-Cu^{+1} enhanced tumor pigmentation and inhibited tumor encapsulation, a characteristic not shared with NTA-Cu^{+2}. Tumors without capsules grew as unrestrained ascites and this was associated with an earlier onset of morbidity and decreased survival. Only mice treated with copper chelates permitted sc tumor takes. Treatment with NC-Cu^{+1} caused a reversible suppression of body weight, indicating that tumors grew slowly and independently of host body weight accretion until treatment was stopped. Treatment with NC-Cu^{+1} enhanced tumorigenicity of sc tumors as evidenced by an earlier onset of palpability, enhanced tumor takes in NIH Swiss mice, decreased final tumor weight and tumor burden, and shortened host survival. These results suggest that copper chelates alter the biological growth characteristics of B16 melanoma in both a murine and copper chelate-specific manner, and that the growth-promoting activity of NC-Cu^{+1} on tumors is related to the oxidation state of copper in chelates and enhanced copper nutriture of tumors. The potentially adverse interaction of elevated plasma copper levels in cancer patients with chemotherapeutic agents is discussed. [Cancer Treat Rep 69:1283–1291, 1985]

Pigmented melanoma cells require copper for activation of tyrosinase, an enzyme responsible for both melanin synthesis (1) and respiratory activity that provides cellular energy in the form of ATP (2,3). Treating syngeneic mice bearing B16 melanoma with copper chelates enhanced tumor pigmentation, promoted malignancy through inhibition of tumor encapsulation, and increased tumor burden, indicating that exogenous copper was detrimental to tumor-bearing mice (4).

Although the mechanisms underlying the growth-promoting activity of exogenous copper on B16 melanoma are unclarified, it would appear that copper serves a dual role in melanoma biology as both an essential nutrient and a pharmacological modulator of immune reactions to tumors. In the latter regard, evidence is accumulating to suggest that copper is one largely unexplored environmental factor that may alter the therapeutic efficacy of anticancer agents. This is evidenced by elevated plasma copper levels in many animal and human malignancies (5–9) and reports from in vitro studies indicating that copper chelates exert synergistic and dose-related inhibition of lymphocyte proliferation and immune responses (10–13).

To provide additional insight into the possible role of

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exogenous copper as an immune modulator affecting melanoma growth in vivo, heterogenetic strains of mice were pretreated with copper chelates before and after inoculation with B16 melanoma cells. It is reported here that exogenous copper in the form of copper chelates greatly improves tumor takes, stimulates tumor growth, and enhances tumor-related morbidity otherwise not observed in untreated heterogenetic mice. This report provides further evidence to suggest that the copper status of patients undergoing chemotherapy is one parameter that should be carefully monitored during the treatment of copper-requiring tumors.

MATERIALS AND METHODS

Chemicals

All chemicals used in this study were reagent grade unless specified otherwise. Cupric sulfate heptahydrate (analytical grade) was purchased from Mallinckrodt, Inc, Paris, KY; sodium ascorbate was purchased from Sigma Chemical Company, St. Louis, MO; neocuproine (NC) was purchased from G. Frederick Smith Chemical Company, Columbus, OH; and nitrilotriacetic acid, disodium salt (NTA), and propylene glycol (analytical grade) were obtained from Aldrich Chemical Company, Milwaukee, WI.

Preparation of Copper Chelates

An injectable solution of NTA-Cu^{+2} was prepared by mixing equal volumes of stock solutions of NTA (40 μmols/kg) and cupric sulfate (20 μmols/kg) dissolved in sterile double-glass-distilled water. The final injectable solution contained a dose of 20 μmols of NTA and 10 μmols of cupric sulfate/kg of mouse body weight. An injectable solution of NC-Cu^{+1} was prepared by mixing equal volumes of stock solutions of NC (30 μmols/kg), cupric sulfate (15 μmols/kg), and sodium ascorbate (30 μmols/kg). The NC solution was prepared by dissolving NC in 25% aqueous propylene glycol solution and the copper sulfate solution was prepared similarly to that described above. Sodium ascorbate solution was also prepared in sterile double-glass-distilled water. The final solution for treating mice contained a dose of 10 μmols of NC, 5 μmols of cupric sulfate, and 10 μmols of sodium ascorbate/kg of mouse body weight. Sodium ascorbate was added last to the solution for reducing cupric copper to the cuprous state. Copper chelates were prepared on the day of injection and used within 1 hour.

Mice

Specific pathogen-free female C57BL/6 mice, male BALB/c × DBA/2 (CDF_1), and male N:NIH(SW) mice (NIH Swiss) were obtained from the Animal Genetics and Animal Production Branch, Division of Cancer Treatment, National Cancer Institute (NCI), Frederick Cancer Research Facility, MD. Mice were 16–18 weeks of age at the time of experimentation. All mouse experiments were performed in the Animal Care Facility of the NCI, Bethesda, MD. Mice were maintained on a 12-hour light-dark cycle, and the room temperature and relative humidity were kept constant at 24°C ± 1°C and 52% ± 5%, respectively. Mice were housed four each to a polycarbonate cage containing sterilized wood chip bedding. Cages were tiered on a stainless-steel cage rack equipped with an automatic central watering and monitorial system (Model CMS-616, Edstrom Industries, Waterford, WI). Mice were allowed free access to diet and tap water at all times. The mouse diet consisted of a natural product mixture that contained 23.5% crude protein, 4.5% crude fat, 4.5% crude fiber, and 7.5% crude ash with vitamin and mineral premixes added according to the specification of the NIH Rat and Mouse Ration product #5018 (Ralston Purina Company, Checkerboard Square, St. Louis, MO). Cupric sulfate was included in the diet formulation at 4 g/2000 lb of final product.

Tumor

A highly pigmented B16 melanoma obtained from the Division of Cancer Treatment Tumor Repository, NCI, Frederick Cancer Research Facility, MD, was used in all experiments. The tumor was maintained in vivo as a sc transplant in female C57BL/6 mice. All tumor suspensions, prepared according to the method of Fidler et al (14), were > 95% viable by trypan blue exclusion tests. Mice received 10^6 viable tumor cells either ip or sc in a fixed volume of 0.1 ml. Tumor volume was calculated from the mean of three individual caliper measurements of tumor diameter using the formula for a hemiellipsoid ($\pi/6 \times \text{mean diameter}^3$). Tumor diameters were measured every other day once tumors were palpable.

Melanoma Experiments

Mice of different strains were divided into experimental groups. Each group contained 12 mice. Some mice received single daily injections of either NTA-Cu^{+2} solution or NC-Cu^{+1} solution every other day for 7 days prior to tumor inoculation on Day 0 and every other day for 15 days posttumor inoculation. Some mice received injections of 0.9% NaCl solution, NTA (20 μmols/kg), NC (10 μmols/kg), or sodium ascorbate (20 μmols/kg) in similar treatment schedules. Untreated tumor-bearing mice and mice administered solutions of either NaCl, NTA, NC, ascorbate, or the solvent vehicle served as control groups. Only the latter control group is reported, since none of the control treatments produced results that differed significantly from the control group receiving the solvent vehicle. All solutions were injected ip in a volume equal to 1% of mouse body weight. The effect of treatment

with copper chelates on melanoma growth characteristics was determined by changes in body weight, survival time, tumor volume, final tumor weight, percent tumor takes, and percent tumor burden. The percent tumor burden represents the percent of final body weight contributed by final tumor weight and therefore is a value dependent on both of these variables and independent of the site of tumor inoculation.

The degree of final tumor pigmentation was scored as highly pigmented, mixed black and grey populations of cells, and mixed grey and amelanotic populations of cells. The presence of tumor capsules in groups inoculated ip with tumor cells was scored by both resistance to puncture with a surgical probe and physical removal of the capsular membrane surrounding tumors.

Statistical Analyses

The data were analyzed by multivariate analysis, and the difference between two means was determined using the least significant difference test (15).

RESULTS

Treatment with either NC-Cu^{+1} or NTA-Cu^{+2} was generally nontoxic to mice when administered during the treatment schedule used here. However, the chelates failed to protect host tissues from copper toxicity when the dose of copper was elevated. Increasing the dose of either NTA-Cu^{+2}, NC-Cu^{+1}, or $CuSO_4$ solution to 30–15, 20–10, or 15 μmols/kg, respectively, was toxic to mice regardless of strain, causing convulsions, hyperactivity, hind-limb paralysis, and, in several cases, intestinal necrosis after 2 days of treatment.

Transplanted tumor cells were rejected after ip inoculation into control CDF_1 mice unless they were pretreated with copper chelates (data not shown in table 1). Treatment with NC-Cu^{+1} enhanced host morbidity as evidenced by approximately 60% decreased survival of CDF_1 mice compared to mice treated with NTA-Cu^{+2}.

Less than one-half of the untreated NIH Swiss mice accepted tumors (table 1). Treatment with NTA-Cu^{+2} more than doubled the number of tumor takes and

TABLE 1.—Effect of copper chelate treatment on the growth characteristics of ip B16 melanomas

Treatment group*	Death range (Days)	Death day (mean ± SE)	Mortality (%)	Tumor takes (%)†	Pigmented tumors (%)‡	Tumor burden (% ± SE)§	Final tumor weight (mean ± SE)	Tumors encapsulated (%)¶
CDF_1 mice								
NTA-CU^{+2}	57–86	73.7 ± 2.8		100.0	41.6	36.4 ± 1.0	15.0 ± 0.5	100.0
NC-Cu^{+1}	24–43	28.3 ± 0.8	61.6**,††	100.0	100.0	24.2 ± 1.3	6.8 ± 0.4††	
NIH Swiss mice								
Control	50–85	67.5 ± 3.5		41.7	100.0	32.6 ± 1.1	13.5 ± 0.5	100.0
NTA-Cu^{+2}	29–80	53.8 ± 4.4	20.3‡‡	91.6	45.5	36.5 ± 1.3	15.6 ± 0.6	100.0
NC-Cu^{+1}	7–23	18.4 ± 1.9	72.7††,‡‡,§§	83.3	100.0	31.0 ± 1.5	11.3 ± 0.7	

*Each group contained 12 mice. Mice received injections of either copper chelates or solvent vehicle every other day beginning 7 days prior to tumor inoculation (Day 0) and for 15 days after tumor inoculation. Control CDF_1 mice rejected transplanted B16 melanoma tumor cells.

$$\dagger\% = \frac{\text{No. of mice exhibiting tumors}}{\text{Total No. inoculated with tumor cells}} \times 100.$$

$$\ddagger\% = \frac{\text{No. of mice exhibiting heavily pigmented tumors}}{\text{Total No. exhibiting tumors}} \times 100.$$

$$\S\% = \frac{\text{Final tumor weight at death (g)}}{\text{Final body weight at death (g)}} \times 100.$$

$$\P\% = \frac{\text{No. of mice exhibiting encapsulated tumors}}{\text{Total No. exhibiting tumors}} \times 100.$$

$$**\% = \frac{\text{Mean Day of death for NTA-Cu}^{+2}\text{ group - NC-Cu}^{+1}\text{ group}}{\text{Mean Day of death for NTA-Cu}^{+2}\text{ group}} \times 100.$$

††Significantly different from NTA-Cu^{+2} group ($P < 0.05$).

$$\ddagger\ddagger\% = \frac{\text{Mean Day of death for control group - NTA-Cu}^{+2}\text{ group}}{\text{Mean Day of death for control group}} \times 100.$$

§§Significantly different from untreated group ($P < 0.05$).

decreased survival by about 20% compared to untreated mice. Treatment with NC-Cu^{+1} dramatically decreased survival by about 70% compared to untreated mice and by about 66% compared to mice treated with NTA-Cu^{+2}. In addition, treatment with NC-Cu^{+1} doubled the number of tumor takes in NIH Swiss mice compared to untreated mice.

The body weight of control CDF_1 mice that completely rejected ip tumor transplantation remained relatively constant at 28 ± 1.2 g throughout the experiment (data not shown in fig 1). The administration of copper chelates had variable effects on body weight. Treatment with NTA-Cu^{+2} did not suppress body weight of CDF_1 mice as did NC-Cu^{+1} and the body weights of CDF_1 mice treated with NTA-Cu^{+2} steadily increased. The body weights of control NIH Swiss mice and those treated with NTA-Cu^{+2} were consistent (fig 2) and paralleled those observed for control mice. Like CDF_1 mice, NIH Swiss mice treated with NC-Cu^{+1} showed suppressed body weights until after the 15-day treatment period ended (figs 1 and 2). After treatment with NC-Cu^{+1} was stopped, the inhibitory influence on body weight was also removed, suggesting that NC-Cu^{+1} caused a reversible suppression of body weight and a cytostatic effect on ip tumors. In addition, the body weight data for both CDF_1 and NIH Swiss mice (figs 1 and 2, respectively) argue against the possibility of sulfate itself as a causative agent, since cuprous sulfate (NC-Cu^{+1}) was more toxic than cupric sulfate (NTA-Cu^{+2}) at a lower sulfate dose.

Treatment with NC-Cu^{+1} increased the number of highly pigmented tumors in CDF_1 mice by more than twofold (table 1). Highly pigmented tumors were found in the small percentage of tumor takes in control NIH Swiss mice. However, treatment with NTA-Cu^{+2} reduced the number of pigmented tumors in NIH Swiss mice despite the enhanced number of tumor takes. Treatment with NC-Cu^{+1} doubled the number of tumor takes in NIH Swiss mice, and the resulting tumors were heavily pigmented.

Treating CDF_1 mice with NC-Cu^{+1} reduced the percent tumor burden (table 1) and this was due to decreased final body weight (fig 1), tumor weight, and the resulting shortened host survival due to enhanced tumorigenicity (table 1). However, treatment with copper chelates had little influence on the percent tumor burden of NIH Swiss mice despite the large variations in host survival. The rapid tumor growth occurring in NIH Swiss mice after treatment with NC-Cu^{+1} was stopped accounted for the consistency of the tumor burden (table 1). This observation suggests that tumor cells remained viable during treatment with NC-Cu^{+1}, but grew slowly without initial accretion of body weight until treatment was stopped.

Treatment with NTA-Cu^{+2} permitted the growth of encapsulated tumors in CDF_1 mice and had little influence on the percent of encapsulated tumors in NIH Swiss mice

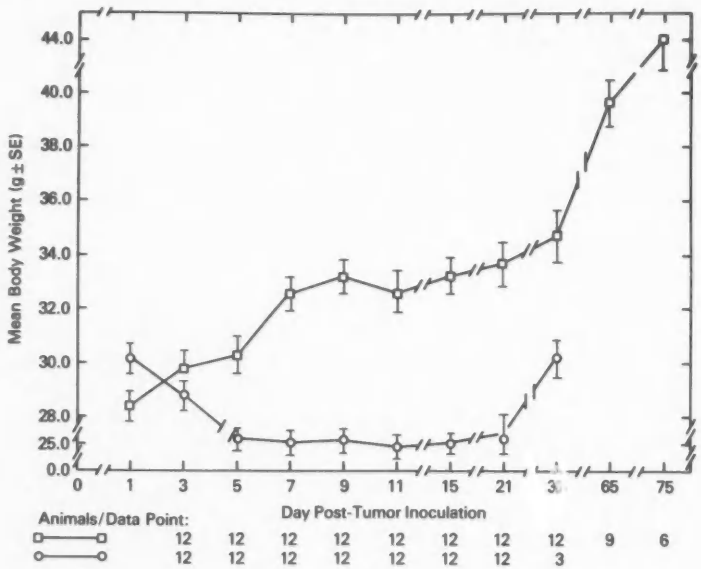

FIGURE 1.—Change in body weight of melanoma-bearing CDF_1 mice treated with copper chelates. Open squares = mice treated ip with NTA-Cu^{+2}; open circles = mice treated ip with NC-Cu^{+1}.

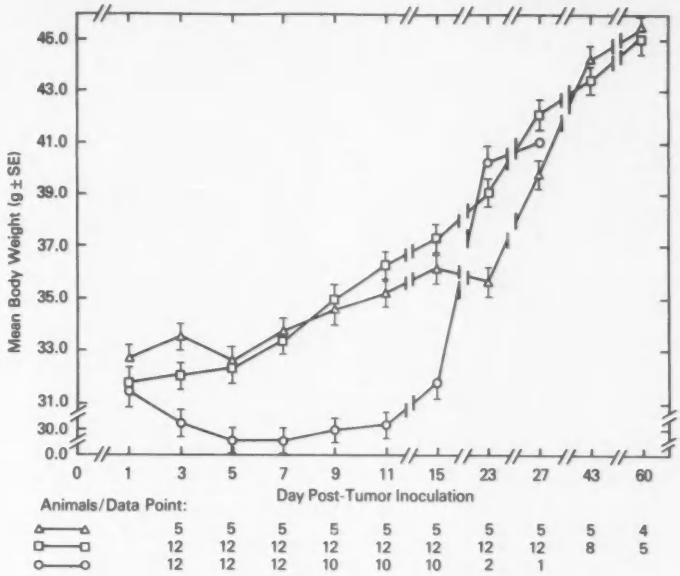

FIGURE 2.—Change in body weight of melanoma-bearing NIH Swiss mice treated ip with copper chelates. Open triangles = untreated mice; open squares = mice treated ip with NTA-Cu^{+2}; open circles = mice treated ip with NC-Cu^{+1}.

compared to control mice (table 1). No detectable tumor capsules were observed in CDF_1 and NIH Swiss mice treated with NC-Cu^{+1}. Tumors without capsules grew as unrestrained ascites in mice treated with NC-Cu^{+1}. The absence of tumor capsules in CDF_1 mice treated with NC-Cu^{+1} generally correlated with shortened tumor growth periods, reduced final tumor weight, and enhanced morbidity. This was not the case for NIH Swiss mice treated with NC-Cu^{+1}, where the absence of tumor capsules correlated with reduced survival but not with reduced final tumor weight. The lack of an inhibitory effect of NTA-Cu^{+2} on tumor encapsulation in NIH Swiss mice, and the lesser effect on both survival and the percentage of tumor takes compared with NC-CU^{+1}, suggests that the differential activities of these copper chelates may not be dose-related.

Treating CDF_1 mice bearing sc tumors with NC-Cu^{+1} decreased survival by > 40% compared to mice treated with NTA-Cu^{+2} (table 2). Transplanted tumor cells were rejected after sc inoculation into control CDF_1 mice unless they were pretreated with copper chelates. Treatment with both NTA-Cu^{+2} and NC-Cu^{+1} permitted 100% sc tumor takes in CDF_1 mice.

Treating NIH Swiss mice bearing sc tumors with NC-Cu^{+1} decreased survival by about 26% compared to mice treated with NTA-Cu^{+2} (table 2). Contrary to the limited number of tumor takes in untreated NIH Swiss mice inoculated ip with tumor cells (table 1), inoculation sc resulted in complete tumor rejection (table 2). This indicated that the sc site in NIH Swiss mice was more inhibitory for tumor establishment than the ip site and that the inhibition was overcome by treatment with copper chelates, particularly by NC-Cu^{+1}, which permitted 100% tumor takes, a characteristic not shared by NTA-Cu^{+2}.

Treatment with NTA-Cu^{+2} had little influence on initial tumor growth rate compared to NC-Cu^{+1} in CDF_1 mice (fig 3), but slightly slowed tumor growth in NIH Swiss mice (fig 4). Treatment with NC-Cu^{+1} permitted earlier appearances of palpable sc tumors in both murine strains.

Treatment with NTA-Cu^{+2} had little effect on pigmentation in tumors growing in CDF_1 and NIH Swiss mice (table 2). These tumors were composed of mixed grey and amelanotic cell populations. However, treatment with NC-Cu^{+1} increased the number of heavily pigmented tumors in both strains, another characteristic not shared by NTA-Cu^{+2} (table 2).

Tumors grew to a very large size in CDF_1 and NIH Swiss mice treated with NTA-Cu^{+2} (table 2 and figs 3 and 4, respectively). However, the percent tumor burden was dramatically decreased in CDF_1 and NIH Swiss mice treated with NC-Cu^{+1} compared to mice treated with

TABLE 2.—Effect of copper chelate treatment on growth characteristics of sc B16 melanomas

Treatment group*	Death range (Days)	Death day (mean ± SE)	Mortality (%)†	Tumor takes (%)‡	Pigmented tumors (%)§	Final tumor weight (mean ± SE)	Tumor burden (% ± SE)¶
CDF_1 mice							
NTA-Cu^{+2}	45–88	63.8 ± 3.7		100.0		14.3 ± 0.6	42.9 ± 1.7
NC-Cu^{+1}	18–44	35.7 ± 2.4**	44.0**	100.0	100.0	8.0 ± 1.0**	26.7 ± 3.1**
NIH Swiss mice							
NTA-Cu^{+2}	47–66	56.3 ± 1.7		58.3		7.8 ± 1.7	20.9 ± 1.3
NC-Cu^{+1}	31–54	41.4 ± 2.1**	26.5**	100.0	100.0	2.9 ± 0.8**	7.5 ± 1.9**

*Each group contained 12 mice. Mice received injections of either copper chelates or solvent vehicle every other day beginning 7 days prior to tumor inoculation (Day 0) and for 15 days after tumor inoculation. Control CDF_1 and NIH Swiss mice rejected transplanted B16 melanoma tumor cells.

$$\dagger\% = \frac{\text{Mean Day of death for NTA-Cu}^{+2}\text{ group - NC-Cu}^{+1}\text{ group}}{\text{Mean Day of death for NTA-Cu}^{+2}\text{ group}} \times 100.$$

$$\ddagger\% = \frac{\text{No. of mice exhibiting tumors}}{\text{Total No. inoculated with tumor cells}} \times 100.$$

$$\S\% = \frac{\text{No. of mice exhibiting heavily pigmented tumors}}{\text{Total No. of mice exhibiting tumors}} \times 100.$$

$$\P\% = \frac{\text{Final tumor weight at death (g)}}{\text{Final body weight at death (g)}} \times 100.$$

**Significantly different from NTA-Cu^{+2} group ($P < 0.05$).

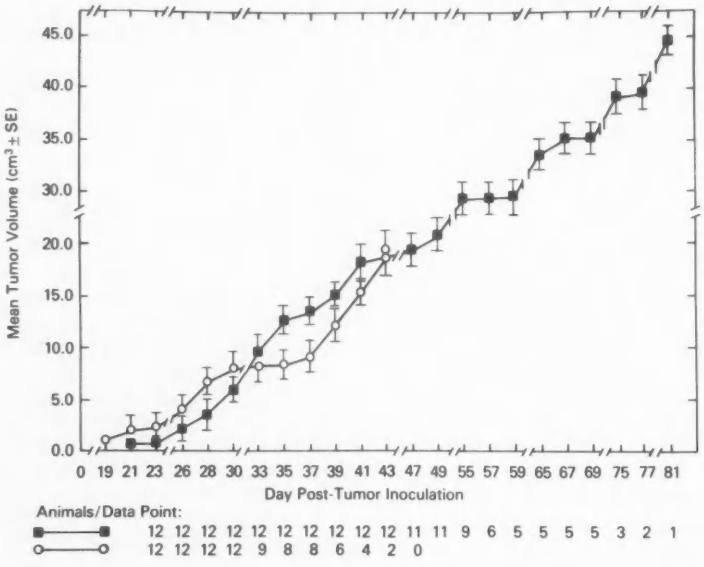

FIGURE 3.—Influence of treatment with copper chelates on sc growth of B16 melanoma in CDF_1 mice. Closed squares = mice treated ip with NTA-Cu^{+2}; open circles = mice treated with NC-Cu^{+1}.

NTA-Cu^{+2}. This was due to enhanced tumorigenicity, which resulted in shortened host survival (table 2).

DISCUSSION

Healthy humans exhibit a mean serum copper level of 100 μg/100 ml, and this level may be increased up to threefold during metastatic disease (5). Serum copper levels > 265 μg/100 ml may be fatal to humans (5). Hence, patients with advanced malignancies may be at risk to chronic copper toxicity, and this may be complicated in part by a heightened nutritional requirement for copper by tumors (5–9). Since overt signs of copper toxicity in mice were not observed with the dosages of copper chelates used here, the modulatory role of exogenous copper on B16 melanoma tumorigenicity may reflect only the result of cumulative increases in body copper.

Previously, observations indicated that the treatment of mice with copper chelates enhanced the tumorigenicity of copper-requiring B16 melanomas in syngeneic mice; one explanation for this was thought to involve altered immune surveillance (4). This possibility prompted the present study where heterogenetic strains of mice were treated with copper chelates before and after tumor inoculation. The results reported herein suggest that copper chelates also enhanced tumorigenicity in heterogenetic strains of mice, which otherwise rejected tumor transplantation, and support an inhibitory role for exogenous copper on immune responses to tumors.

The mechanism by which treatment with copper chelates improved tumor takes in CDF_1 and NIH Swiss mice may involve inhibition of T-cell-mediated immunity, which is sensitive to exogenous copper, especially when it is chelated (10–13). In addition, exogenous copper in the form of NC-Cu^{+1} further enhanced tumor takes in NIH Swiss mice and hastened host mortality. This observation supports a vital role for exogenous copper in copper-requiring melanoma cells (4), and suggests that NC, which is known to deliver copper to cells (16), may enhance tumorigenicity directly by supplying essential copper and indirectly by concomitantly inhibiting the immune system.

One explanation for tumor rejection by CDF_1 mice lies in histocompatibility. The CDF_1 strain is a murine hybrid produced by BALB/c female and DBA/2 male parents (17). Since CDF_1 mice rejected melanoma transplantation here and DBA/2 mice were previously shown to readily accept transplanted B16 melanoma tumors (4), the histocompatibility of the maternal genotype largely governs tumor rejection unless it is otherwise inhibited by treatment with copper chelates. However, the observation that only ip and not sc tumors were accepted as transplants in untreated NIH Swiss mice additionally suggests that the site of tumor inoculation may be another factor

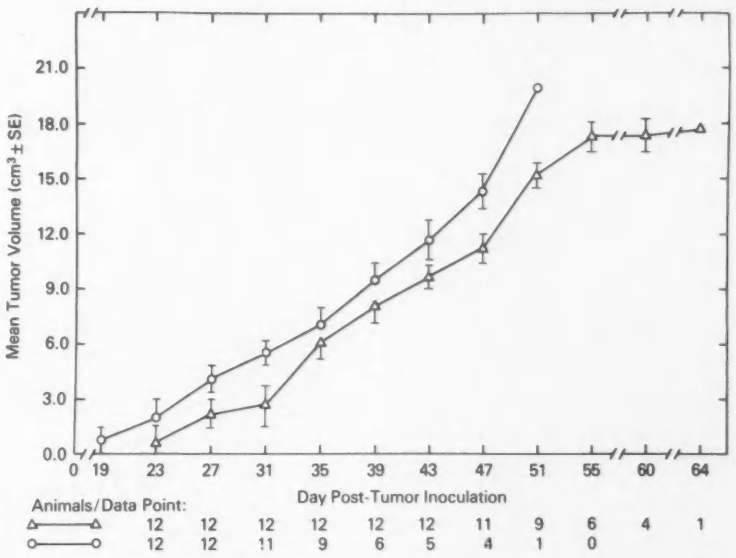

FIGURE 4.—Influence of treatment with copper chelates on growth of B16 melanoma in NIH Swiss mice. Open triangles = mice treated with NTA-Cu^{+2}; open circles = mice treated ip with NC-Cu^{+1}.

governing tumorigenicity and as such is related to nutrient availability (18,19) and immune responses to tumors (20-23).

Tumors grew as unrestrained ascites in CDF_1 and NIH Swiss mice treated with NC-Cu^{+1}, indicating that this copper chelate either prevented tumor encapsulation and/or rapidly stimulated tumor growth and subsequent host mortality prior to tumor encapsulation (table 1). Treatment with NTA-Cu^{+2} had little influence on tumor encapsulation, further suggesting that NC-Cu^{+1} and NTA-Cu^{+2} exerted different biological effects on melanoma growth characteristics. The inhibitory influence of treatment with NC-Cu^{+1} on tumor encapsulation in syngeneic mice bearing B16 melanomas was also previously observed (4).

The responses of tumor-bearing mice to treatment with copper chelates shown here suggest that both the oxidation state of copper and the copper-delivering capacity of each chelate are important variables modulating melanoma growth. Although the treatment with both chelates dramatically improved the number of tumor takes in CDF_1 and NIH Swiss mice, it was particularly evident that the treatment with NC-Cu^{+1} was more tumorigenic in NIH Swiss mice bearing sc tumors, which showed almost twofold more tumor takes than mice treated with NTA-Cu^{+2} (table 2).

In addition, NTA-Cu^{+2} was also found to be tumorigenic, suggesting that B16 melanoma cells may be obtaining copper through other mechanisms independent of selective copper delivery by chelates. Such a mechanism might involve the induction of hepatic ceruloplasmin synthesis by exogenous copper (24); the selective transfer of copper from ceruloplasmin to tumor cells (25); and the induction of tumor metallothionein for binding copper in a manner analogous to that found for many metals (26).

Once copper enters a melanoma cell it may be used as a prosthetic group in tyrosinase and thereby stimulate melanogenesis (27). However, little is known about the regulatory role of exogenous copper in this regard other than reports on the inhibition of melanoma tyrosinase activity by other chelating agents like D-penicillamine (28) and diethyldithiocarbamate (29) or through dietary restriction (30). The results presented here suggest that exogenous copper has a differential role in the regulation of melanoma tyrosinase activity in that only the treatments with NC-Cu^{+1} enhanced tumor pigmentation. Moreover, the murine strain used to grow melanomas and the site of tumor inoculation are additional factors influencing the pigmentation of murine B16 melanoma.

Although there was little change in the initial growth rate of sc tumors in CDF_1 mice treated with NC-Cu^{+1}, close examination of the sc tumors at necropsy indicated that tumor size was largely influenced by an accumulation of bloody fluid. This was not observed in CDF_1 mice treated with NTA-Cu^{+2} where sc tumors grew as solid masses. However, a similar observation was found with NIH Swiss mice treated with NC-Cu^{+1}, but not with syngeneic mice (4). Collectively, these observations suggest that the modulatory role of NC-Cu^{+1} on melanoma growth is dependent on the site of tumor inoculation and the murine strain supporting the tumor. Thus, NC-Cu^{+1} can function as a growth-promoting agent enhancing tumorigenicity and host mortality and as a potential toxin that selectively decreases final sc tumor weight in heterogenetic mice.

Therefore, the differential response of murine melanoma growth to treatment with copper chelates suggests that the copper status of the tumor-host interrelationship is a critical factor governing the biological behavior of melanoma cells in vivo. Since plasma copper levels have long been known to be elevated in patients with malignant melanoma and other cancers (5-9), special care should be considered with the choice of chemotherapeutic agents for treating patients, avoiding those drugs and/or their derived metabolites having a propensity for complexing with and then delivering copper to copper-requiring tumors. Moreover, certain environmental and physiological factors are capable of elevating serum copper in humans. Sources of exogenous copper capable of elevating serum levels include: drinking water; handling, preparing, and storing foods; smoking; hemodialysis; and various disease states both directly and indirectly associated with malignancies (5).

It is important to note that the chelating agents used here may not be metabolized in a manner resembling other drugs. However, future studies could be aimed (*a*) at understanding the potentially adverse interaction of copper with drugs and their metabolites already in use for treating melanoma patients and (*b*) at the design of new agents that selectively alter copper homeostasis and interfere with copper utilization by copper-sensitive tumors.

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Potentiation and Protection of Doxorubicin Cytotoxicity by Cellular Glutathione Modulation[1]

Angelo Russo and James B. Mitchell[2,*]

One of the proposed mechanisms of doxorubicin cytotoxicity is generation of activated oxygen species, all of which are either free radical or potentially free radical species. Glutathione is an intracellular sulfhydryl-containing tripeptide that is known to detoxify free radicals and the damage they produce. The cytotoxicity of doxorubicin was evaluated following treatment with agents that will either elevate intracellular glutathione (2-oxothiazolidine-4-carboxylate) or deplete intracellular glutathione (D,L-buthionine-*S,R*-sulfoximine). Our results show that intracellular glutathione levels correlate with doxorubicin cytotoxicity, ie, elevated glutathione provides protection and decreased glutathione levels increase cytotoxicity. These results are discussed in the context of cardiac toxicity as well as enhancing tumor cell kill with doxorubicin. [Cancer Treat Rep 69:1293–1296, 1985]

Anthracyline antibiotics such as doxorubicin and daunorubicin have proven clinical utility in the treatment of cancer (1). There are both acute and chronic toxic effects associated with their use (2). The major chronic toxicity is myocardial dysfunction (2), which necessitates cessation of drug usage beyond 550 mg/m^2. The mechanisms of antineoplastic activity and myocardial toxicity may be different (3–5). The etiology of myocardial toxicity is not fully understood, yet a growing body of information suggests generation of activated oxygen species with subsequent toxic redox cycling as the final common pathway that promotes cardiocellular toxicity (6). Glutathione (GSH) is an intracellular detoxifying agent for inactivation and repair of free radical species (7); therefore, it seems reasonable to study the effect of GSH modulation on the cytotoxicity of doxorubicin. Cellular GSH concentrations in this study were modulated by depletion with D,L-buthionine-*S,R*-sulfoximine (BSO), which specifically inhibits GSH synthesis (8), or elevation of GSH by 2-oxothiazolidine-4-carboxylate (OTZ), which stimulates GSH synthesis (9).

MATERIALS AND METHODS

Cell culture.—Chinese hamster V79 cells were grown in F12 medium supplemented with 10% fetal calf serum (Grand Island Biological Company, NY), penicillin G potassium (0.14 g/L), and streptomycin (0.2 g/L). Exponentially growing stock cultures were maintained at 37°C in a humified atmosphere of 5% CO_2 and 95% air. Cell survival was assayed using standard in vitro plating efficiency techniques. The plating efficiency ranged from 0.80 to 0.95 for all studies. The pH of the culture medium was maintained at 7.2–7.4 for all studies.

Chemicals.—Concentrated stock solutions of doxorubicin, supplied by the Drug Synthesis and Chemistry Branch, National Cancer Institute, were diluted in methanol and stored at 4°C for ⩽ 3 weeks. BSO was obtained from Chemalog, South Plainfields, NY, and dissolved in complete medium. OTZ was synthesized as previously described (10).

Drug exposure.—Exponentially growing cells from stock flasks were trypsinized (0.03% trypsin and 0.01% EDTA), counted, and approximately 8×10^5 cells were plated into a number of 100-mm Petri dishes and incubated overnight. Following the incubation period (12–16 hours), the medium was removed and replaced with either complete medium containing varying concentrations of doxorubicin or drug-free medium for control conditions and incubated for 1 hour at 37°C. The drug levels

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of doxorubicin used were within the range of clinically achievable plasma levels. Following drug exposure, the plates were rinsed twice with a phosphate-buffered solution (0.9% NaCl) (PBS), trypsinized, counted, and appropriate numbers of cells plated for macroscopic colony formation. Some studies required pretreatment with BSO or OTZ. BSO (10 mM) or OTZ (10 mM) in complete medium was added 4 or 2 hours, respectively, prior to doxorubicin exposure and incubated at 37°C. Following pretreatment, the medium was removed and replaced with medium containing doxorubicin and the respective pretreatment drug at the concentration cited above. Therefore, for studies involving BSO and OTZ, both drugs were also present during the doxorubicin exposure. Following the various experimental protocols, the dishes were incubated at 37°C for 7–10 days, after which colonies were fixed, stained with crystal violet, and counted. Experiments for each protocol were repeated two to three times and were in qualitative agreement. The results shown are from single experiments where the individual experimental points were plated in triplicate. The error bars on the charts represent the standard deviation and are shown when larger than the symbol size.

GSH assay.—For each survival study, parallel dishes were plated for GSH concentration determinations. Following various treatments, the cells were trypsinized, washed twice with cold PBS, counted, resuspended in 2 ml of cold sulfosalicylic acid, lysed via sonication, and then centrifuged at 4°C. The cold supernatant was removed and assayed for total GSH content by the GSH reductase procedure (11). GSH levels for control cells ranged from 0.5 to 1.0 $\mu g/10^6$ cells. Bars on the chart symbols represent the standard deviation and are shown when larger than the symbols.

RESULTS

Cellular GSH levels were modulated by continuous exposures to drugs which either inhibit (BSO) or stimulate (OTZ) the GSH biosynthetic pathway. The total cellular GSH concentration (expressed as a percentage of control values) as a function of the time of exposure to these drugs is shown in figure 1. Exposure of cells to BSO results in GSH depletion because the rate of GSH utilization exceeds the resynthesis. BSO treatment of V79 cells results in a gradual reduction in GSH concentration (open triangles) so that after 4 hours of exposure, GSH levels are 5% of control values. There was no appreciable effect on the plating efficiency of cells treated with 10 mM BSO for the time intervals used in these studies. Conversely, exposure of cells to OTZ promotes elevation in GSH levels (open circles). The elevation in GSH of OTZ-treated cells was verified to be enhanced GSH biosynthesis by simultaneous exposure of cells to OTZ and BSO. BSO inhibits GSH synthesis by blocking the synthesis of gamma-glutamylcysteine; therefore, the simultaneous addition of BSO and OTZ would be expected to result in complete cessation of GSH synthesis, unless there was disulfide interchange between cysteine (the product of OTZ metabolism) and a GSH/protein disulfide. Figure 1 shows that exposure of cells to OTZ and BSO resulted in no increase in GSH, thereby verifying that the GSH elevation following OTZ alone did not result from disulfide interchange, but rather is the result of synthesis alone.

Survival curves for cells exposed to various concentrations of doxorubicin for 1 hour are shown in figure 2. Figure 2A illustrates the effect of GSH depletion by BSO on doxorubicin survival. BSO-treated cells were clearly more sensitive to doxorubicin, particularly at the higher concentrations. Dose-modifying factors for BSO-treated cells at a doxorubicin concentration of 1.0, 3.0, or 5.8 μg/ml were 4.0, 10.5, and 9.0, respectively. When GSH levels were elevated prior to doxorubicin exposure by OTZ, protection was observed (fig 2B). The protection was observed for all dose levels of doxorubicin exposure. Dose modifying factors for OTZ-treated cells at a doxorubicin concentration of 1.0, 3.0, or 5.8 μg/ml were 5.0, 5.5, and 3.0, respectively.

DISCUSSION

A considerable interest has been shown in doxorubicin-induced free radical production, particularly in relation to cardiac toxicity (5,6,12,23). Because of this, we have studied the effects of both GSH depletion (BSO) (8) and elevation (OTZ) (9). In hepatocytes with GSH levels reduced to < 20% in the presence of a specific inhibition of the GSH-regenerating enzyme glutathione reductase,

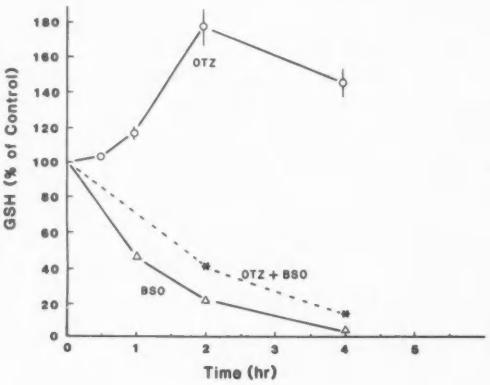

FIGURE 1.—Cellular GSH levels [expressed as % of control values for cells continuously exposed to 10 mM BSO (△), 10 mM OTZ (○), or 10 mM BSO + 10 mM OTZ (●)] in complete medium.

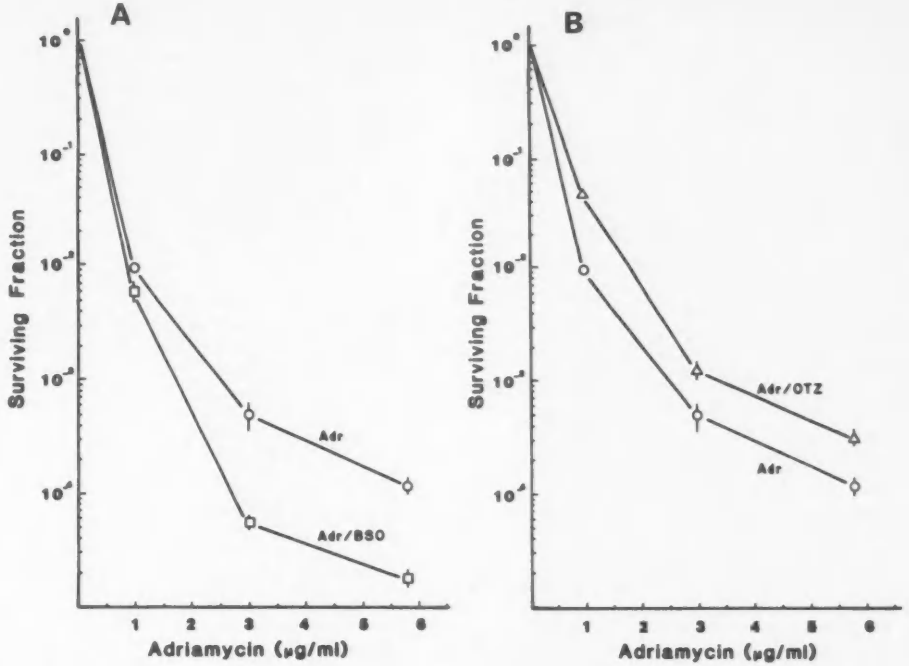

FIGURE 2.—Cell survival curves for exposure to various concentrations of doxorubicin for 1 hr. A. ○ = doxorubicin alone; □ = cells pretreated for 4 hrs with 10 mM BSO, then exposed to doxorubicin. GSH levels for BSO-treated cells just prior to doxorubicin exposure were < 5% of control values. B. ○ = doxorubicin alone; □ = cells pretreated for 2 hrs with 10 mM OTZ, then exposed to doxorubicin. GSH levels for OTZ-treated cells just prior to doxorubicin exposure were approximately 180% of control values.

doxorubicin cytotoxicity is increased (14). Furthermore, the use of the general sulfhydryl trap (DEM) has been shown in an in vivo system to increase cardiac toxicity of doxorubicin (13,15). Since there is now available a more specific blocker of an enzyme in the GSH synthesis pathway (in particular, BSO, an irreversible inhibitor of gamma glutamylcysteine synthetase), the potential of exploring the effects of selective GSH depletion is now more feasible. Studies have already shown that BSO causes cell sensitization to several different chemical and physical assaults (16–20).

Recently, BSO has been used to deplete GSH in conjunction with subsequent doxorubicin treatment; the results of the study reportedly showed no increased cytolysis (21). This is surprising and may result from differential responsiveness in different cell lines, or in the time required to achieve GSH depletion, as well as the techniques used to interpret the results. Particularly, there are difficulties in extrapolating to clonogenicity or altered reproductive integrity using methods such as trypan blue dye exclusion, which is more specifically a method to determine cell membrane damage, and thereby only indirectly a method reflecting ultimate cell survival (22). The data published on hepatocytes indicate that GSH depletion without the ability to synthesize new GSH is toxic. Our results with BSO depletion are consistent with these data, as well as work done with BSO, when used to enhance H_2O_2 kill (16,19), ie, we see sensitization.

Therefore, we sought to selectively elevate GSH levels without exposing cells to extracellular thiols, thereby obviating possibly misleading effects that might occur from exogenously applied sulfhydryl groups in the extracellular milieu, such as oxidation of the applied sulfhydryl group (23), in situ generation of free radical species, and depletion of oxygen. In OTZ, the sulfhydryl that is intracellularly unmasked enzymatically by cleavage of the thiazolidine ring, ie, cysteine, directly feeds into the GSH cycle (9). Furthermore, previous work has shown OTZ to lessen toxicity associated with GSH depletion and reactive metabolite-induced damage (9). Our work further suggests that there may be a use of OTZ in doxorubicin-associated toxicity, particularly in light of the work done with *N*-acetylcysteine that showed there were differences in cardiac toxicity at 330 mg/m^2 but not at

550 mg/m^2 (24). In part, the explanation for the decreased efficacy at higher cumulative doxorubicin doses could be attributed to poor patient compliance because of the emetic effect of *N*-acetylcysteine. OTZ has a masked sulfhydryl group and therefore the well-known odiferous nature of free sulfhydryl group containing compounds can be avoided.

While several mechanisms for doxorubicin cytotoxicity have been proposed, our work is consistent with an aspect of the cytotoxicity being caused by free radical or electrophilic-induced damage and fits well within the framework of doxorubicin-induced free radical reactions that are scavenged by sulfhydryl compounds.

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Treatment of Chronic Myelogenous Leukemia in Blastic Crisis With Chemotherapy Incorporating Vindesine-Prednisolone[1]

Yoshiro Uzuka* and Yoshiko Saito[2]

Twenty-three patients with chronic myelogenous leukemia (CML) in terminal transformation were treated with a regimen incorporating vindesine (a new derivative of vinblastine), prednisolone, and additional cytarabine. Of 21 patients in blastic crisis, complete remission (CR) was achieved in 15 (71.4%). All of five patients with lymphoid morphology and ten of 12 with myeloid morphology (83.3%) achieved CR, while none of four with monocytoid morphology achieved CR. Two patients in accelerated phase also attained CR. Our results compare favorably with those of other regimens in this refractory disorder and indicate that the regimens incorporating vindesine, prednisolone, and additional cytarabine may be recommended in the treatment of CML-blastic crisis with both lymphoid and myeloid morphology and accelerated phase of CML as well. [Cancer Treat Rep 69:1297–1299, 1985]

Although patients with chronic myelogenous leukemia (CML)-blastic crisis (BC) with lymphoid morphology, hypodiploid cytogenetics, and terminal deoxynucleotidyl transferase (TdT) activity may have an improved response to treatment with a combination of vincristine and prednisolone, the overall remission rate has consistently remained < 30% and the median survival has been < 6 months (1-3). The present report documents the effects of vindesine-prednisolone (VDS-P) and vindesine-cytarabine-prednisolone (VDS-CP) therapy in the treatment of CML-BC.

MATERIALS AND METHODS

Twenty-three patients in the terminal phase of CML were studied. Of these patients, 21 were in BC and two were in the accelerated phase. There were 16 males and seven females, with an age range of 19–71 years (median, 32). The diagnosis of BC was based on the presence of > 20% blast cells in the bone marrow and/or > 30% of the sum of myeloblasts and promyelocytes in the peripheral blood. Cytomorphological subclassification of blast cells was established by the results of May-Gruenwald stain, cytochemical staining, and cell surface marker analysis.

The chemotherapy schedules are shown in figure 1. The schedules and dosages were individually modified according to the patient's response to therapy and the degree of drug toxicity. In all patients, at least four doses of vindesine were administered before they were considered to be nonresponsive. When complete response (CR) was not achieved within 28 days, their induction therapy was extended for an additional 2 weeks, and the patients treated with VDS-P were given additional doses of cytarabine.

CR was defined as < 5% myeloblasts in either the normocellular or the hypercellular bone marrow in addition to regression of all abnormal physical signs. Partial remission was defined as the reduction of marrow blast cells to < 20% as well as regression of abnormal physical signs.

RESULTS

Morphological Characteristics

Five patients had lymphoid morphology, 12 had myeloid morphology, and four had monocytoid morphology.

Chemotherapeutic Responsiveness

All patients were treated for 3–4 weeks before determining the maximum therapeutic benefit or before abandoning the treatment as ineffective. CR was achieved in two patients in accelerated phase and in 15 (71.4%) of the

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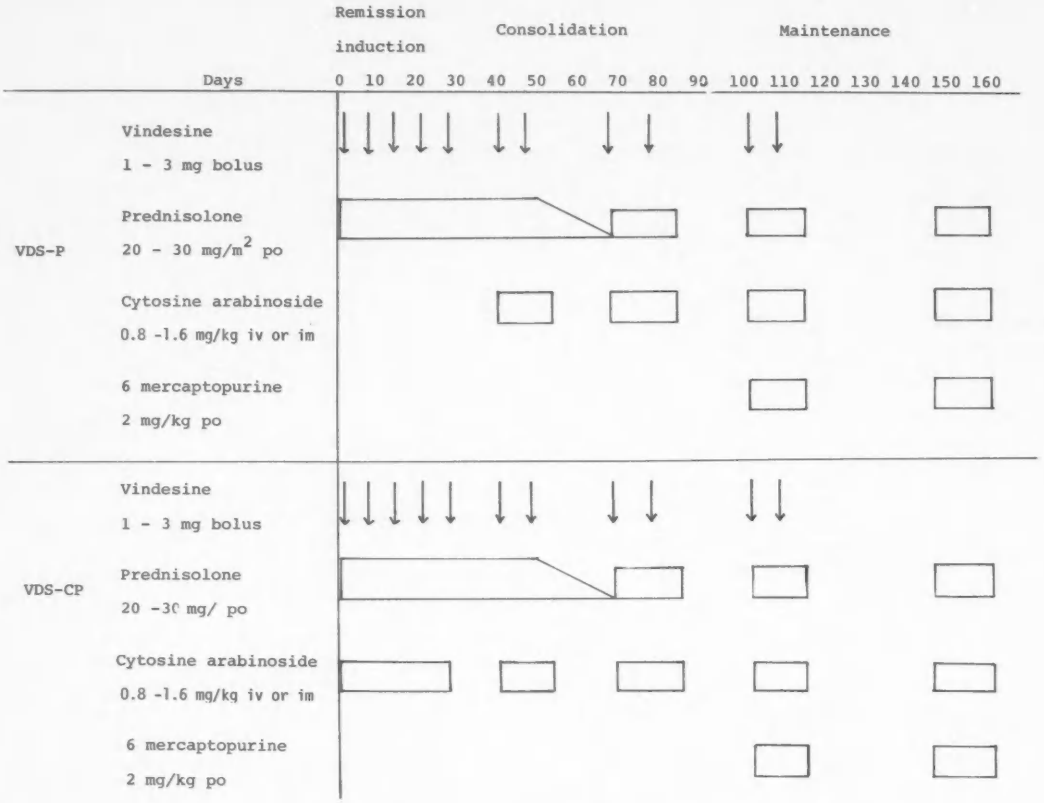

FIGURE 1.—Treatment schema of CML-BC.

21 patients in BC. All five patients with lymphoid morphology and ten of 12 (83.3%) with myeloid morphology achieved CR by the administration of either the VDS-P or VDS-CP regimen, while none of the four patients with monocytoid morphology achieved CR. Both TdT-positive patients and three of five TdT-negative patients achieved CR using VDS-P. Three of four TdT-negative patients treated with VDS-CP also achieved CR. Ten of 15 complete responders received consolidation therapy, and six received maintenance therapy.

The duration of CR ranged from 5 to 107 weeks (median, 19). The survival from the onset of BC ranged from 3 to 159 weeks (median, 29) for the entire group of patients.

The median time from the initiation of therapy to CR was 29 days in all complete responders. All complete responders developed marrow depression, and in nine patients the decrease of wbc count to $< 1000/mm^3$ and marrow nucleated cell count to $< 15,000/mm^3$ was observed (table 1). The main manifestation of toxicity consisted of hematological and neurological side effects. However, because of the low cumulative dose of vindesine, no neurotoxicity was observed in this series.

DISCUSSION

Canellos (1) reported CR in six of 30 patients with CML-BC using vincristine and prednisone and later confirmed these results in a larger group of patients. The combination therapy of vincristine and prednisolone was effective in about one-third of the patients with CML-BC and especially in those of lymphoid type (1-4). It seems reasonable to substitute vincristine with a less neurotoxic drug, vindesine. The CR rates obtained by the groups using combination therapy of vindesine and prednisone ranged between 11.1% and 48.5% (5). In comparison with a more aggressive chemotherapy protocol (6), the CR rates were in a similar range. Our study demonstrated that the regimen incorporating VDS-P, and in particular, additional cytarabine, had significant activity

TABLE 1.—Response to VDS-P in patients with CML-BC

	No. of patients	Course No.					Days to CR			Maximum myelosuppression			
		1	2	3	4	5	Range	Median	Mean	Wbc count nadir		Nucleated cell count nadir	
										Range	Median	Range	Median
Complete responder	15	14	1	0	0	0	14-53	29	30.7	300-3000	1200	4600-28,000	11,200
Partial responder	6	5	1	0	0	0	1	1	1	844-31,500	1000	1400-158,000	34,100

in the treatment of patients with lymphoid BC and myeloid BC as well. The effects of vindesine seemed to be superior to those of vincristine, and vindesine was effective even in vincristine-resistant patients. The short remission duration was, however, disappointing. To improve the results, remission induction with the more aggressive regimen of VDS-CP was studied. This regimen presented progress in the treatment of CML-BC. The aims of our future studies are to elucidate the treatment regimen for consolidation and maintenance therapy in CML-BC.

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Comparison of the Antiemetic Efficacy of Two High-Dose Benzamides, Metoclopramide and Alizapride, Against Cisplatin-Induced Emesis[1]

Reinhard Saller* and Dieter Hellenbrecht[2]

The antiemetic effect of two benzamides, metoclopramide (MCL; Paspertin) and alizapride (AZP; Vergentan), was compared in two double-blind sequential analytical trials in cisplatin-treated patients (60–90 mg/m^2). In the first trial, the drugs were given as loading infusions (0.5 mg/kg of body weight/hour over 2 hours) beginning 2 hours before cisplatin administration; the maintenance infusion (0.25 mg/kg/hour) given over 24 hours was half the dose (total dose, 7 mg/kg of body weight per treatment cycle). In the second trial, the dose of AZP was doubled. After nine and ten treatment pairs, MCL was significantly ($2P < 0.10$) more effective than AZP: three of nine and four of ten patients receiving MCL remained totally free from vomiting, compared with only none of nine and one of ten patients receiving AZP. The incidence of extrapyramidal reactions was similar in all treatments. However, the administration of AZP was much more unfavorable because of moderate to severe hypotensive side effects. [Cancer Treat Rep 69:1301–1303, 1985]

The effectiveness of high-dose metoclopramide (MCL) in the prevention of cisplatin-induced emesis has been repeatedly demonstrated (1). A novel congener of MCL, alizapride (AZP), has been claimed to exert strong antiemetic activity against chemotherapy-induced emesis (2). However, there are few clinical data comparing AZP with standard treatments, eg, MCL (3). This investigation addresses the relative antiemetic effectiveness and the associated adverse effects. Because of the large doses and the expected frequency of adverse reactions, the sample size was to be as small as possible. Sequential analysis of matched pairs was therefore used as experimental design (4–6).

MATERIALS AND METHODS

Thirty-eight patients (ages 41–68 years; 16 tumors of lung, 22 tumors of head and neck) gave informed consent. Patients with creatinine clearances < 60 ml/minute, brain or liver metastases, or anticipatory emesis were excluded. No patients received sedatives, hypnotics, opiates, antidepressant agents, or neuroleptic drugs. All patients received loperamide (2 mg every 6 hours) as antidiarrheal therapy. All patients were hydrated with 1000 ml/hour for 2 hours, followed by fluids at a rate of 250 ml/hour for 24 hours. Patients fasted for the first 12 hours. After the first 2 hours of hydration, cisplatin (60–90 mg/m^2, together with bleomycin or vindesine) was administered over 30–60 minutes.

MCL (MCL I, II) was given as a loading dose of 0.5 mg/kg of body weight/hour over 2 hours, and was subsequently given as a maintenance dose of 0.25 mg/kg/hour over 24 hours (total doses per cycle are shown in table 1). The dosage for AZP was the same

TABLE 1.—Frequency of episodes of emesis per cycle of cisplatin therapy for the two sequential trials*

	Pair No.—										
	1	2	3	4	5	6	7	8	9	10	Mean
MCL I	1	1	2	2	0	1	0	3	0		1.1
AZP I	5	3	7	2	6	5	8	7	4		5.2
MCL II	2	0	1	0	0	3	2	1	0	1	1.0
AZP II	2	5	3	1	0	4	5	4	3	4	3.1

*MCL I, II = 7 mg/kg of body weight/cycle; AZP I = 7 mg/kg of body weight/cycle; and AZP II = 14 mg/kg of body weight/cycle.

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TABLE 2.—Adverse reactions per drug and drug dosage

	MCL I	AZP I	MCL II	AZP II
Sedation	5	6	5	6
Akathisia	4	4	3	3
Dystonia	2	1	2	2
Rigor	2	2	2	3
Hypotension				
Systemic blood pressure 100–90 mm Hg	1	3	0	3
Systemic blood pressure < 90 mm Hg	0	1	0	3
Blurred vision	0	1	0	2

(AZP I) or double (AZP II) as for MCL. To evaluate the efficacy and risk of the treatments, a standardized questionnaire was used. Patients were entered in the study sequentially: two consecutive patients were treated as a pair and were randomized by tossing a coin to one of the two drugs previously assigned to set pair, ie, MCL I/AZP I (nine pairs) or MCL II/AZP II (ten pairs). A 2-α level of 0.10 was taken as the level of significance (4). The number of episodes of emesis (ie, number of forceful expulsions separated by free intervals) was counted for each of the two members of a pair by an independent observer over 26 hours after cisplatin. Neither observers nor patients were informed about the treatment regimen used. The treatment causing fewer episodes of emesis among the treatment pairs was considered superior.

RESULTS

The mean number of emetic episodes (table 1) during both MCL treatments was only 1.1 and 1.0, respectively. The antiemetic potency of AZP was markedly lower, resulting in 5.2 mean emetic episodes per patient at the lower dose, and 3.1 at the higher dose. Two or fewer episodes of vomiting, a clinically acceptable and useful result, were found in eight of nine and nine of ten patients receiving MCL, but in only three of nine and four of ten patients receiving AZP. Nausea was mild more often with MCL I and II, compared to AZP I or II. One patient receiving AZP II required anticholinergic treatment with iv biperiden after sustained rigor.

Table 2 lists the frequency of adverse reactions. The incidence of sedation and extrapyramidal reactions (ie, acute dystonia, akathisia, rigor) was comparable with both drugs. However, there were significantly more moderate and severe hypotensive reactions in the higher-dosed AZP II group [no events with MCL II vs six events with AZP II, $2P < 0.05$, Fisher's exact test (6)].

DISCUSSION

The results of this study show a threefold to fivefold lower frequency of emetic episodes in patients treated with MCL compared to patients treated with AZP, and no differences in the incidence of extrapyramidal reactions. It is concluded that the clinical outcome of the study is clearly in favor of MCL. The frequency of extrapyramidal reactions did not increase with doses of AZP. Similar results can be seen in the data of patients treated with even higher doses of AZP (7). For MCL, we have seen a similar absence of dose-dependency of extrapyramidal reactions (unpublished observations). Therefore, this seems to be a common phenomenon for antiemetic drugs of the benzamide type. Even higher doses of MCL may be administered, if necessary (eg, up to 15 mg/kg/cycle), without risk of dose-dependent drug accumulation (1,8). For AZP, severe hypotensive effects may be dose-limiting. This has also been observed by other investigators (9).

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Carboplatin: A New Platinum Analog in the Treatment of Epidermoid Carcinoma of the Esophagus[1,2]

Cora Sternberg,[3] David Kelsen,[3,*] Mary Dukeman,[3] Lawrence Leichman,[4] and Robert Heelan[3]

Thirty-one patients with advanced epidermoid carcinoma of the esophagus were treated with carboplatin (CBDCA), a second-generation cisplatin analog. Thirty patients were evaluable for response. Major responses (complete response) were seen in two patients (7%; 95% confidence limits, 1%–20%). The median survival from initiation of the protocol was 3 months (range, 0.1–16). Neither renal dysfunction nor emesis was a significant problem with CBDCA; hematologic toxicity was dose-limiting. Thrombocytopenia was more marked than leukopenia. CBDCA is a well-tolerated cisplatin analog that produced two complete responses in patients with advanced epidermoid carcinoma of the esophagus, where such responses are rarely observed. Although the observed response rate was only 7%, the 95% confidence limits overlap those previously reported for cisplatin (12%–31%). [Cancer Treat Rep 69:1305–1307, 1985]

Carboplatin (CBDCA) is a second-generation cisplatin analog that was designed to have a broader therapeutic index, lack of cross-resistance, and less nephrotoxicity and to be at least as active as the parent compound. In preclinical testing, CBDCA demonstrated activity against various tumor lines (1). In phase I clinical studies, the maximum tolerated dose was 520 mg/m^2 when given iv every 4 weeks (2). Reversible myelosuppression, particularly thrombocytopenia, was the dose-limiting toxic effect. Nephrotoxicity was minimal as determined by urine assays for renal tubular damage. Mild nausea and vomiting were encountered. The recommended dose for phase II trials was 400 mg/m^2 (3). Activity was seen in ovarian carcinoma, lung cancer, testicular seminoma, and mesothelioma (4–6), with minimal activity in gastric adenocarcinoma (7). Cisplatin has modest activity in epidermoid carcinoma of the esophagus (ECE), with substantial toxicity. A phase II trial with CBDCA in patients with this disease was performed.

MATERIALS AND METHODS

Thirty-one patients with metastatic, recurrent, or unresectable ECE received CBDCA. Protocol eligibility required a measurable or evaluable (ie, primary tumor) indicator lesion that had not been recently irradiated, Karnofsky performance status $\geq$ 50%, wbc count $\geq$ 4000/mm^3 and platelet count $\geq$ 150,000/mm^3, serum bilirubin $\leq$ 1.5 mg/100 ml, BUN $\leq$ 30 mg/100 ml, serum creatinine $\leq$ 1.5 mg/100 ml and/or creatinine clearance $\geq$ 50 ml/minute/1.73 m^2, normal auditory function, and informed consent.

CBDCA (400 mg/m^2 every month) was given iv over 1 hour with 500 ml of 5% dextrose in one-half normal saline before and after therapy. In patients with prior therapy, the starting dose was decreased to 300 mg/m^2 due to thrombocytopenia. A cbc was obtained on Days 7, 14, and 21, with dose escalation by 50 mg/m^2, for a wbc count nadir $\geq$ 3000/mm^3 and a platelet count nadir $\geq$ 150,000/mm^3. CBDCA was postponed pending recovery of the wbc count to $\geq$ 3000/mm^3, the platelet count to $\geq$ 150,000/mm^3, and the creatinine to $\leq$ 1.5 mg/100 ml and/or creatinine clearance to $\geq$ 50 ml/minute/1.73 m^2.

For patients with measurable lesions (eg, lymph nodes or subcutaneous masses, pulmonary lesions, and hepatic masses), the response criteria of Miller et al were used (8). For patients in whom the primary esophageal tumor was the indicator lesion, criteria for response were those pre-

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[2]Carboplatin was synthesized by the Johnson Matthey Research Centre, Sonning, England, and formulated by the Bristol Myers International (Laboratoire Allard, Nogent-sur-Marne, France).

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viously published (9). If the barium esophagram returned to normal, a repeat endoscopy with negative washings and brushings was required before the patient was considered to be in complete remission (CR). Duration of response was measured from initiation of protocol.

RESULTS

Characteristics of the patient population studied are shown in table 1, with 30 patients evaluable for response. One patient was considered inevaluable after review of the barium esophagram failed to reveal an indicator lesion. Two patients achieved CR (7%; 95% confidence limits, 1%-20%), and one had minor regression lasting 2.5 months. Neither responding patient had received prior chemotherapy. The median survival from initiation of the protocol was 3 months (range, 0.1-16).

One patient achieved CR for 7 months, with disappearance of multiple hepatic nodules, the largest of which measured 7 × 5 cm. A second patient with bronchoscopically proven tracheal invasion by esophagoscopy and bronchoscopy achieved CR that lasted for 16 months and died of other causes.

Renal dysfunction was not a significant problem, with only two patients having an elevation in creatinine > 2.0 mg/100 ml. The median peak creatinine was 1.0 mg/100 ml (range, 0.7-2.3). Hematologic toxicity was substantial. Thrombocytopenia was more marked than leukopenia, with a median platelet count nadir of 146,000/mm^3 (range, 14,000-410,000). The median time to nadir counts was 21 days. While there was no difference in nadir counts based on prior chemotherapy or irradiation, nine of 14 patients with prior irradiation had received a lower dose of 300 mg/m^2. Other toxic effects included nausea and vomiting, which were infrequent, and auditory dysfunction (one patient).

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	31
Evaluable	30
Males:females	18:13
Median age in yrs (range): 63 (41-77)	
Median Karnofsky performance status (range): 70% (50%-90%)	
Indicator lesion	
Primary tumor	12
Liver	2
Nodes	2
Lung	5
Masses on physical examination	10
No prior chemotherapy	20 (65%)
Prior chemotherapy	11 (35%)
Cisplatin	11
+ 5-FU	3
+ vindesine + bleomycin	4
+ vindesine + mitoguazone	4
Prior irradiation, 3000-6000 rads (median, 5000)	14 (45%)

DISCUSSION

No single agents have reliably produced a major objective response rate of > 25% in ECE, and CRs are rare. Following the initial report of the activity of cisplatin and bleomycin, four trials of cisplatin alone were reported. A total of 73 patients were treated with a variety of doses and schedules, with an overall response rate of 22% (95% confidence limits, 12%-31%) and a 2-3-month median duration of response (10).

Cisplatin has been included in most multidrug combinations used in ECE, with response rates varying from 15% to 80%. The largest series, from Memorial Hospital, of cisplatin, vindesine, and bleomycin observed a response rate of 53% in 68 patients (11). Cisplatin produces substantial nausea and vomiting, decreased auditory acuity, neurotoxicity, and dose-limiting nephrotoxicity. All of these side effects are less frequently encountered in patients treated with CBDCA. The major toxic effect in this trial was myelosuppression, which occurred at the third week, with thrombocytopenia more prevalent than leukopenia.

Although the response rate was quite modest, it was similar to that seen with cisplatin. Two CRs, which were fairly durable, were observed in patients with ECE, where such responses are rarely observed. CBDCA is a well-tolerated cisplatin analog that warrants further study in combination with other agents.

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Metoclopramide in Vincristine-Induced Ileus[1]

Harinder S. Garewal[2,3] and William S. Dalton[3,*]

Three cases of vincristine-induced gastrointestinal toxicity were treated with metoclopramide. Two patients had severe abdominal pain and adynamic ileus, while the third had severe constipation and abdominal bloating. Rapid resolution of symptoms occurred in all three patients. Metoclopramide may, therefore, prove useful in the treatment of these not infrequent toxic effects of vinca alkaloids. [Cancer Treat Rep 69:1309–1311, 1985]

The vinca alkaloids, vincristine and vinblastine, are among the most useful anticancer drugs available. Neurotoxicity is a frequent side effect of these agents, usually manifest as a dose-related, peripheral, sensorimotor neuropathy (1–3). The gastrointestinal tract is often affected, and the earliest symptoms of neurotoxicity may be colicky abdominal pain and constipation. These can occur in up to 30%–40% of patients receiving these drugs (2,3). The constipation may be severe and can lead to fecal impaction. Very severe cases may present as an acute abdomen with diminished or absent bowel sounds and radiographic findings of an adynamic ileus. No specific drug is available for treatment of vinca-induced gastrointestinal toxicity. Metoclopramide is known to increase gastrointestinal tract motility with activity on the esophagus, stomach, and small intestine (4). Consequently, this drug was given to three patients who had severe gastrointestinal toxicity from vincristine. All of these patients showed marked improvement within 24 hours of initiating treatment.

CASE REPORTS

Patient 1

A 62-year-old man with chronic granulocytic leukemia with recent lymphoblastic transformation was begun on vincristine and prednisone. He received 2 mg of vincristine iv and had abdominal pain on follow-up 1 week later. A reduced dose of vincristine (0.5 mg) was, therefore, given on Day 7. Four days later he presented to the emergency room with severe abdominal pain, having no bowel movement since the last clinic visit. Abdominal radiographs showed dilated loops of bowel, suggestive of adynamic ileus. Nasogastric suction was started, but with no improvement in symptoms or ileus over 24 hours (fig 1A). Metoclopramide (20 mg iv every 4 hours) was begun. The patient noted marked relief of abdominal pain within 4–6 hours of starting metoclopramide and began to have bowel movements shortly thereafter. The metoclopramide was switched to a "prn" schedule after 24 hours. As a result, he did not receive any metoclopramide for the next 24 hours and again began having abdominal discomfort. Metoclopramide was restarted on a regular schedule (every 4 hours iv) with rapid resolution of symptoms. The nasogastric tube was removed, resolution of ileus confirmed radiographically (fig 1B), and the patient started on a clear liquid diet which was rapidly advanced to a regular diet over 24 hours. The patient was discharged on oral metoclopramide (20 mg four times a day) which was discontinued 1 week later without recurrence of symptoms. He refused further treatment for his underlying disease and eventually died.

Patient 2

A 43-year-old man with acute lymphoblastic leukemia was begun on vincristine and prednisone as part of induction therapy for his disease. He was scheduled to receive 2 mg of vincristine iv every week. He had diffuse abdominal pain 3 days after his second vincristine injection. He had not had any bowel movement over the preceding 24 hours. On examination, he was found to be in marked distress and hypotensive. The blood pressure responded rapidly to iv fluids. Bowel sounds were initially hyperactive, but over the next 4–6 hours became hypoactive, and finally were absent. Abdominal radiographs showed dilated loops of bowel consistent with adynamic ileus.

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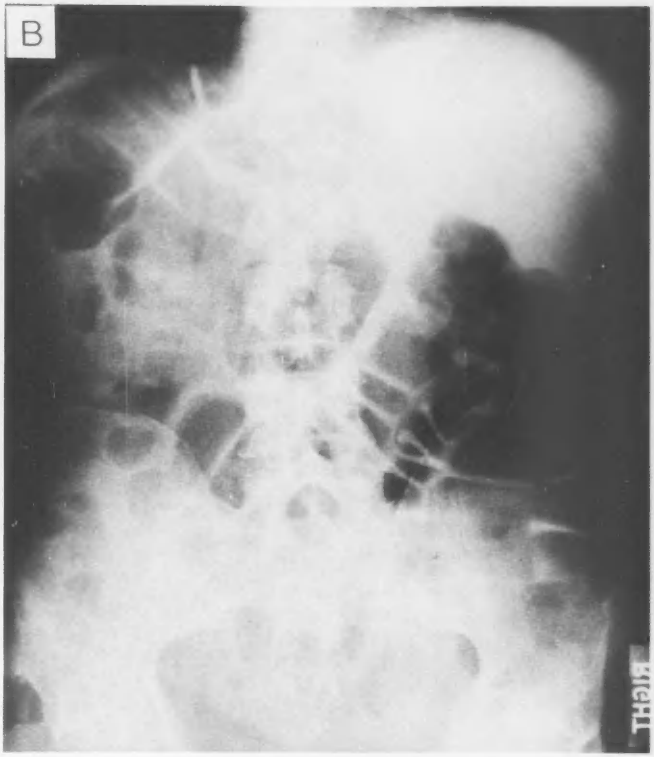
FIGURE 1.—A. Upright abdominal radiograph (Pat
Upright abdominal radiograph (Patient 1) after n



raph (Patient 1) prior to beginning metoclopramide. B.
1) after metoclopramide.

Nasogastric suction was begun and the patient started on metoclopramide (10–20 mg iv every 6 hours). The patient's abdominal symptoms improved over the next 6–8 hours, and he began having bowel movements on the following day. Resolution of the ileus was documented by radiography. Nasogastric suction was discontinued and oral intake begun. Since vincristine was considered to be an essential part of his chemotherapeutic regimen, oral metoclopramide was continued through the remainder of his induction therapy. He did not experience any recurrence of the abdominal pain, despite additional vincristine.

Patient 3

A 71-year-old man with chronic lymphocytic leukemia continued to be anemic while being treated with chlorambucil alone. Vincristine and prednisone were, therefore, added to his chemotherapy. Approximately 3 days after receiving his first dose of vincristine (2 mg iv), he began having abdominal bloating, early satiety, and constipation. The latter did not respond to multiple enemas and laxatives that the patient used on his own. On examination his abdomen was minimally distended. Bowel sounds were diminished. A diagnosis of vincristine-induced gastroparesis was made and metoclopramide was given. An initial iv dose was given in the clinic, followed by oral doses to be taken at home. The patient had bowel movements beginning on the day of metoclopramide administration, with resolution of his abdominal bloating and early satiety symptoms.

DISCUSSION

Decreased gastrointestinal motility is a common manifestation of vinca neurotoxicity (2,3). Usually manifest as constipation, it can on occasion present with symptoms of an acute abdominal catastrophe with adynamic ileus. Standard treatment for this has consisted of nasogastric suction with resolution of the ileus over several days. No specific drug is available to hasten the resolution of this syndrome.

We have used metoclopramide to treat three patients with vincristine-induced gastrointestinal toxicity, with rapid resolution of symptoms. Two of the three patients presented with severe abdominal pain and adynamic ileus. The third patient had severe constipation and abdominal bloating. The rapid resolution of symptoms in all three patients suggests that the drug may indeed be useful in treating this syndrome. In Patient 1, symptoms recurred after metoclopramide was not given for 24 hours, with prompt resolution on restarting a regular schedule.

We have not treated any patient with vinblastine-induced gastrointestinal symptoms. Since the mechanism involved is likely to be similar to vincristine, metoclopramide may also prove useful with vinblastine.

Since metoclopramide is contraindicated in bowel obstruction, this diagnosis must be ruled out prior to its use. This is usually not a problem since the clinical evidence, including time of onset of symptoms in relationship to drug administration, is sufficient to make a diagnosis of drug-induced ileus in most patients.

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Phase II Trial of 5-FU, Vincristine, and Mitomycin (FOMi) in Metastatic Bronchioloalveolar Cell Lung Cancer: A Southwest Oncology Group Study[1,2]

Thomas P. Miller[3] and Robert B. Livingston[4,*]

Twenty-three previously untreated patients with bronchioloalveolar cell lung cancer who had measurable disease and distant metastases (stage IIIM1, extensive) were treated with combination chemotherapy including 5-FU, vincristine, and mitomycin. Two of 23 patients (9%) achieved partial response lasting 5 and 6 months. Two patients (9%) died of sepsis while neutropenic. The current study does not justify the use of 5-FU, vincristine, and mitomycin combination chemotherapy in patients with metastatic bronchioloalveolar cell lung cancer. [Cancer Treat Rep 69:1313–1314, 1985]

Bronchioloalveolar cell lung cancer is probably a distinct clinical and pathologic disease (1). The efficacy of treatment for metastatic disease using single agents or combination chemotherapy is unknown (2). The disease is relatively infrequent and consequently most trials of chemotherapy include very small numbers of patients. Based on reports of some activity of the combination of 5-FU, vincristine, and mitomycin (FOMi) in patients with metastatic adenocarcinoma of the lung (3,4), the Southwest Oncology Group tested the FOMi regimen in a phase II study in 23 patients with bronchioloalveolar cell lung cancer.

PATIENTS AND METHODS

Twenty-three previously untreated patients with bronchioloalveolar cell lung cancer who had measurable disease and distant metastases (stage IIIM1, extensive) were treated with combination chemotherapy using FOMi. Treatment with FOMi consisted of 5-FU (300 mg/m^2/day on Days 1-4); vincristine (2.0 mg on Day 1); and mitomycin (10 mg/m^2 on Day 1). Drugs were administered iv as a slow push. FOMi was repeated every 3 weeks for three courses and then every 6 weeks. The initial doses of chemotherapy were reduced by 33% in patients with presumed inadequate bone marrow reserves and included patients > 65 years of age and patients with extensive bone marrow involvement with tumor. Dose adjustments of drugs were made based on the peripheral blood cell counts obtained at the time treatment was scheduled. The doses of FOMi were decreased by 50% if the wbc count was < 2000/μl and the platelet count was < 75,000/μl or if treatment was delayed by > 2 weeks to allow recovery of the wbc count to ⩾ 3000/μl and the platelet count to ⩾ 100,000/μl. Patients were treated until disease progression or unacceptable toxicity. Initially, abnormal studies were repeated with each course of FOMi to gauge response. Partial response (PR) was defined as a ⩾ 50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions and maintained for at least 6 weeks. All eligible patients were considered evaluable. Patients lost to follow-up (one patient) and those dying before follow-up (three) were considered to have progressive disease.

RESULTS

Patient characteristics and results of treatment are shown in table 1. Two of 23 patients (9%) achieved PR lasting 5 and 6 months. An additional patient had objective regression in tumor measurements, but less than that defined for PR. Both responding patients had an initial Southwest Oncology Group (SWOG) performance status (PS) of 0-1 (Karnofsky, 70-100). The median duration of survival for all patients from the

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TABLE 1.—Results of treatment

Clinical characteristic	PR*	Median survival (wks)
All	2/23 (9)	24
PS, 0-1	2/18 (11)	34
PS, 2-3	0/5 (0)	4
Full doses	1/15 (7)	20
Reduced doses	1/8 (12)	22

*No. of PRs/No. of patients (%).

time of diagnosis was 38 weeks; from the time of first metastases was 30 weeks; and from the time of initiating FOMi was 24 weeks. All 23 patients have died.

Serious toxicity was limited to myelosuppression and suspected drug-induced pulmonary fibrosis. Two patients died of sepsis while neutropenic. Only three additional patients demonstrated myelosuppression as measured on Day 1 of each treatment course. These patients had leukocyte counts between 2000 and 3000/μl. Two patients developed clinical signs of pulmonary fibrosis including progressive dyspnea, nonproductive cough, intermittent low-grade fevers, and radiographic features of fibrosis. Neither patient had a lung biopsy and the suspicion of pulmonary fibrosis was not confirmed. These patients presumably died of progressive lung cancer.

DISCUSSION

FOMi demonstrates modest activity against metastatic bronchioloalveolar cell lung cancer. The 9% response rate in 23 patients (95% confidence interval, 0%-21%) is probably lower than our previous experiences in patients with adenocarcinoma of the lung (3,4). However, whether the lower response rate is due to inherent tumor resistance to FOMi or to higher tumor burdens in this group is unclear. The median survival of 24 weeks after starting treatment is not different than our previous experience with comparably staged patients with adenocarcinoma. The disease is uniformly fatal after metastases develop. It is unclear why a relatively large fraction of patients developed serious toxicity. In our previous larger experience within the SWOG using FOMi for adenocarcinoma and large cell undifferentiated carcinoma, none of 147 patients treated with FOMi died of sepsis, and only one developed toxicity compatible with pulmonary fibrosis (4). The current study with 9% response rates and death rates from treatment does not justify the use of FOMi in patients with metastatic bronchioloalveolar cell lung cancer.

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Phase II Study of Aclarubicin in Patients With Lymphoma[1,2]

Delvyn C. Case, Jr,* Marjorie A. Boyd, and Daniel M. Hayes[3]

Aclarubicin, a new anthracycline antibiotic with less cardiotoxicity relative to doxorubicin, was utilized in 33 patients with advanced lymphoma at a dose of 100 mg/m² iv every 3 weeks. Five patients developed partial response (2, 2, 2, 4, and 8+ months). None of the patients who had received prior anthracycline responded to aclarubicin. The dose-limiting toxic effect was hematologic. One of ten patients having serial measurements of cardiac function had a significant reduction in left ventricular function, but cardiac symptoms did not occur. [Cancer Treat Rep 69:1315–1316, 1985]

Aclarubicin (ACM), a new anthracycline antibiotic, has been shown in preclinical studies to be one-half as potent as doxorubicin, with one-tenth the cardiotoxic effect (1-4). Studies utilizing a daily dose schedule have reported responses as high as 50% in lymphoma (5). In a series utilizing an intermittent schedule, an 8% response rate was observed (6). The present series was developed to define the response rate utilizing an intermittent schedule in patients with lymphoma (7).

METHODS

Patients were eligible for this protocol if they failed or relapsed after initial therapy utilizing at least one multidrug combination. Standard pretreatment evaluation was performed. Left ventricular ejection fraction (LVEF) was measured prior to therapy (8); patients with a resting LVEF of < 50% were excluded. LVEF determination and ECG were repeated every three to four cycles. Informed consent was given before starting therapy. Standard remission criteria were used (8).

The initial dose of ACM was 100 mg/m² every 3 weeks, with escalation of the dose by 20 mg/m² in the absence of hematologic toxicity. The dose of ACM was diluted in 100 ml of 5% dextrose solution and infused iv over a half-hour period.

RESULTS

Thirty-three patients with lymphoma were entered in this protocol. The pretreatment characteristics are shown in table 1. Fifteen of the 33 patients had previously received an anthracycline. The median dosage of ACM administered was 200 mg/m² (range, 100–800); the median number of doses received by patients was two (range, one to 12). Of the 33 patients treated, there were five partial responses (15%): two patients with diffuse poorly differentiated lymphocytic lymphoma and three with nodular poorly differentiated lymphocytic lymphoma. The duration of response was generally short: 2, 2, 2, 4, and 12+ months. None of the five patients who responded had previously received anthracycline.

The dose-limiting toxic effect of ACM was hematologic. The median wbc count nadir was 2500/mm³ (range, 200–16,000), and the median platelet count nadir was 103,000/mm³ (range, 6000–522,000). Myelosuppression persisted for a median of 7 days and occurred at Days 7–14. Nausea and vomiting was seen in most patients (17 of 33). LVEF determinations and ECGs were serially repeated in ten patients who received two or more doses. One patient had a fall in the LVEF from 59% to 44% after 400 mg/m². The patient did not have any cardiac symptoms nor did the ECG change. One patient had a myocardial infarct 3 months after ACM and had been discontinued; the total dose was 200 mg/m². One patient had a myocardial infarct 1 week after 100 mg/m² of ACM. ACM did not appear to contribute to the cardiac symptoms in the latter two patients.

DISCUSSION

The present results are similar to a recent study also

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[2]Presented in part at the Phase II Meeting, Investigational Drug Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, Dec 1983.

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TABLE 1.—Characteristics of patients with lymphoma treated with ACM*

Characteristic	No. of patients
Median age in yrs (range): 68 (31-81)	
Median performance status (range): 80 (50-100)	
Median No. of prior chemotherapeutic regimens (range): 2 (1-4)	
Median No. of prior chemotherapeutic agents (range): 6 (4-10)	
Histologic subtypes	
Diffuse histiocytic lymphoma	9 (9)
Nodular poorly differentiated lymphocytic lymphoma	9
Diffuse poorly differentiated lymphocytic lymphoma	4 (1)
Nodular mixed histiocytic-lymphocytic lymphoma	2
Nodular histiocytic lymphoma	2
Diffuse well-differentiated lymphocytic lymphoma	2
Diffuse mixed histiocytic-lymphocytic lymphoma	1 (1)
Lymphoblastic lymphoma	2 (2)
Hodgkin's disease	2 (2)

*Values in parentheses = No. of patients in each category previously receiving an anthracycline.

utilizing an intermittent schedule (6). None of the patients in the present study who had received a prior anthracycline responded to ACM. In the patients who had not previously received an anthracycline, the response rate was 30%. These data suggest that ACM does share cross-resistance with other anthracyclines. Significant cardiotoxicity was not noted in this study. Only one patient had a significant drop in the LVEF from baseline. No ECG changes or cardiac symptoms developed in this patient. These results are comparable to initial preclinical studies (2,4) and other phase II trials (6,9). The intermittent schedule offers a poor response rate in patients with lymphoma. Because of the limited number of patients with Hodgkin's disease treated in this study, these results may not apply to Hodgkin's disease.

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Continuous-Infusion Vindesine in Refractory Carcinoma of the Cervix: A Phase II Trial[1,2]

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Vindesine is a synthetic vinca alkaloid that is an analog of vinblastine sulfate. Like vinblastine sulfate, vindesine causes mitotic arrest in metaphase by binding to tubulin (1). When vindesine is given as a continuous infusion, it achieves a relatively constant level in serum in 24 hours. A similar dose given as an iv bolus is undetectable in serum at 48 hours (2).

Vindesine has been given to a small number of patients with squamous cell carcinoma of the cervix. Schmohl (3) recorded a response in four of six patients. Vermorken et al (4) noticed a response rate of 24% among 21 evaluable patients who were on a weekly iv bolus schedule. We report here results obtained using vindesine administered as a continuous infusion to treat patients with refractory carcinoma of the cervix.

MATERIALS AND METHODS

Thirty patients with locally recurrent or metastatic squamous cell carcinoma of the cervix received vindesine (table 1). The drug was given by a continuous infusion over a 5-day period. The therapy was repeated every 21–28 days, depending on hematologic recovery. All patients received therapy on an outpatient basis via central venous lines, usually by portable infusion pumps.

The initial dose of vindesine for patients who were considered good-risk candidates for this treatment was 1.0 mg/m^2 per 24-hour period. Patients who had a history of pelvic radiation therapy or of infected pelvic recurrences were considered poor risks and received 0.8 mg/m^2 per 24-hour period. Dose escalations were in 0.2-mg/m^2 increments. Therapy was aimed at producing granulocytopenia with a nadir of 1.0 × 10^3 cells/mm^3. Patient characteristics are described in table 1.

RESULTS

Of the 30 patients entered in the study, two were inevaluable. One of the patients had a major protocol violation. The patient's initial course of therapy was interrupted for a delivery of local radiation therapy. Another patient did not receive the drug after protocol registration. Twenty-eight patients received 84 courses of

TABLE 1.—Patient characteristics

Characteristics	No. of patients (%)
Total evaluable	28 (100)
Mean age in yrs (range): 43 (31–70)	
Performance status (Zubrod)	
0	1 (4)
1	16 (57)
2	9 (32)
3	2 (7)
Prior chemotherapy (No. of regimens)	
0	3 (11)
1	17 (61)
2	6 (21)
⩾ 3	2 (7)
Metastatic sites	
Central/pelvic	19 (68)
Lung	8 (29)
Abdomen	5 (17)
Lymph node	8 (29)
Bone	2 (7)
Granulocyte count nadir (× 10^3 cells/mm^3)	
Median: 1.0	
Range: 0.03–6.5	
Courses ⩽ 1.0–39 (59%)	
Courses ⩽ 0.5–12 (14%)	

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[2]Vindesine was supplied by Lilly Research Laboratories, Indianapolis, IN.

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therapy. The median number of courses per patient was three. Two patients had stabilized disease for 11 and 12 months. The remaining patients had progressive malignancy.

Dosage escalation commonly occurred during the trial. Eleven of 15 patients who started vindesine at the lower dose of 0.8 mg/m^2 had their doses escalated to 1.0 mg/m^2. Four of these were further increased to doses of $\geq$ 1.2 mg/m^2. Of 13 patients who started at doses of 1.0 mg/m^2, four received subsequent courses at doses of $\geq$ 1.2 mg/m^2.

Side effects included mild constipation in seven (25%) and mild neuropathy in nine (32%) patients. The median nadir platelet count of study patients was 254 × 10^3 cells/mm^3. The dose-limiting toxicity was neutropenia, with a median nadir granulocyte count of 1.0 × 10^3 cells/mm^3 (table 1). Five patients (18%) did not develop significant neutropenia during therapy. Four patients (14%) had nadir granulocyte counts between 500 and 1000 cells/mm^3. Twelve patients (44%) had nadir granulocyte counts < 500 cells/mm^3 while on vindesine. Seven patients (25%) developed an infection that required hospitalization. One patient died with neutropenia and fever while suffering bronchial obstruction from progressive malignancy. No patient developed septicemia related to an infected pelvic recurrence of malignancy.

Thus, we conclude that vindesine given as a 5-day continuous infusion to patients with refractory squamous cell carcinoma of the cervix has no antitumor activity and is associated with substantial neutropenia.

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Phase II Trial of 4′-Deoxydoxorubicin in Patients With Advanced Breast Cancer[1,2]

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4′-Deoxydoxorubicin (25 mg/m² iv every 3 weeks) was evaluated in 20 patients with advanced breast cancer. The patients had good performance status and had not been heavily pretreated. Although all patients experienced leukopenia, no major therapeutic responses were observed. Nonhematologic toxicity was mild. Further evaluation of 4′-deoxydoxorubicin at this dose and schedule is not warranted in patients with advanced breast cancer. [Cancer Treat Rep 69:1319–1320, 1985]

4′-Deoxydoxorubicin (dxdx) is a synthetic anthracycline with antitumor activity similar to that of doxorubicin in both animal tumor systems (1) and the human stem cell tumor assay (2). In animals, dxdx showed no cardiac toxicity at doses that produced antitumor effects (1). Phase I evaluation indicated that 25–30 mg/m² administered iv every 3 weeks was an appropriate dose for additional clinical studies (3). Because of the established efficacy of doxorubicin in the treatment of breast cancer, we conducted this phase II trial of dxdx in patients with metastatic breast cancer who had not previously received anthracyclines.

PATIENTS AND METHODS

Twenty patients with advanced breast cancer were studied (table 1). All patients had measurable disease; Karnofsky performance status ⩾ 60%; wbc count ⩾ 4000/mm³; platelet count ⩾ 150,000/mm³; normal renal, hepatic, and cardiac functions; and gave signed informed consent. Sixteen patients had received prior chemotherapy; of these, six had received adjuvant chemotherapy only.

Dxdx was administered iv every 3 weeks. The initial dose was 25 mg/m². A cbc was required between Days 10 and 14 after treatment. Subsequent doses were increased by 5 mg/m² if the wbc and platelet counts remained ⩾ 4000/mm³ and ⩾ 150,000/mm³, respectively. If the wbc count nadir was < 2000/mm³ or the platelet count nadir was < 75,000/mm³, the subsequent dose was decreased by 5 mg/m². A physical examination, including measurement of indicator lesions, was performed every 3–4 weeks. In addition, a serum biochemical profile (BUN, SGOT, LDH, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, inorganic phosphorus, and calcium) was obtained very 3–4 weeks. Other diagnostic evaluations, including x-rays and radionuclide scans, were repeated monthly as required to assess therapeutic response. Standard criteria for response and toxicity were employed (4). The trial was designed using a three-stage multiple-testing procedure (5).

RESULTS

All patients were evaluable. A median of two courses per patient (range, one to five) was administered. Eighteen of the twenty patients received two or more courses. Three patients had their dose escalated by 5 mg/m² for at least one dose, and eight patients required a dose reduction of 5 mg/m² for at least one dose.

No objective therapeutic responses were seen, although nine patients showed no change in disease parameters for a median of 4.0 months (range, 1–5).

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TABLE 1.—Characteristics of 20 patients with breast cancer treated with dxdx

Characteristic	No. of patients
Entered and evaluable	20
Median age in yrs (range): 56 (39–75)	
Median Karnofsky performance status (range): 75% (60%–90%)	
Sites of measurable metastases	
Lymph nodes	7
Skin and subcutaneous	7
Lung	8
Liver	5
Receptor status*	
ER-positive	4
ER-negative	10
ER unknown	6
Prior systemic therapy	
None	3
Hormones only	1
Chemotherapy†	16
CMF only	3 (1 adjuvant)
CMFVP only	12 (5 adjuvant)
CMF + mitomycin	1
Prior radiation therapy	14

*ER = estrogen receptor.

†CMFVP = cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone.

Leukopenia was the major toxic effect observed and was experienced by all patients. The median wbc count nadir was 1900/mm^3 (range, 400–3200). Thrombocytopenia occurred in 40% of the patients (median platelet count nadir, 164,000 cells/mm^3; range, 16,000–297,000 cells/mm^3). Nausea occurred in 70% of the patients, but only 25% had vomiting. Slight hair loss was noted in 50% of the patients. Neither mucositis nor phlebitis was observed, and extravasation of drug did not occur during this study.

No patients developed congestive heart failure. Seven patients had both baseline and follow-up cardiac gated blood pool scans after a minimum of two doses (median total dose, 55 mg/m^2; range, 45–120 mg/m^2); no patients showed a significant decline (≥ 10%) in left ventricular ejection fraction (LVEF) at rest or failed to increase LVEF with exercise on their repeat scans.

CONCLUSION

These patients had good performance status and had not been heavily pretreated. The majority of indicator lesions were either skin or lymph node metastases. Bone lesions were not used as measurable parameters of disease in these patients; therefore, the lack of response cannot be attributed to slow healing of bone lesions that might have become obvious if therapy had been continued. The wbc count nadir range and median indicate that higher doses could not have been administered safely. Furthermore, a clear dose-response relationship has not been demonstrated for doxorubicin in patients with breast cancer.

The response rate to doxorubicin in patients with similar pretreatment characteristics is approximately 30% (6). A similar response rate should be expected from an active doxorubicin analog.

In this study, the hypothesis that the response rate to dxdx is at least 20% was rejected (size = 0.06, power = 0.86); a 95% confidence interval for the response rate to dxdx based on multiple-stage testing is 0%–16% (7). We conclude that at the dose and schedule administered, dxdx has not demonstrated sufficient activity in the treatment of patients with advanced breast cancer to warrant further evaluation.

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Phase II Trial of Mitoxantrone in Multiple Myeloma: A Southwest Oncology Group Study[1,2]

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Thirty-five fully evaluable patients with advanced multiple myeloma, refractory to standard chemotherapeutic agents, were entered into a phase II trial with mitoxantrone at a starting dose of 12 mg/m² iv every 3 weeks. There was one (3%) partial response (lasting 2½ months) in a patient who had received treatment with five different agents, including doxorubicin (total dose, 150 mg/m²). Four additional patients (11%) showed objective evidence of clinical improvement, lasting 4–7 months. Mitoxantrone was well-tolerated with no drug-induced deaths and only moderate to severe leukopenia as the dose-limiting toxicity in the majority of patients. Although mitoxantrone had a low level of activity in this heavily pretreated patient population, consideration should be given to future trials incorporating mitoxantrone into a new drug combination. [Cancer Treat Rep 69:1321–1323, 1985]

Drug treatment of advanced multiple myeloma is extremely limited in patients whose disease has become refractory to standard chemotherapy, including the alkylating agents melphalan, cyclophosphamide, and carmustine; the anthracycline doxorubicin; the vinca alkaloid vincristine; and prednisone (1). In recent phase II studies, mitoxantrone, a new anthracene compound, has been proven to have a relatively high degree of activity in drug-refractory patients with breast cancer (2,3), acute nonlymphocytic and lymphocytic leukemias (4,5), as well as non-Hodgkin's lymphomas of unfavorable histology following primary treatment (6,7). Because of its relative lack of cross-resistance with alkylating agents, anthracyclines, vinca alkaloids, and prednisone, a phase II trial of mitoxantrone was initiated in the Southwest Oncology Group to evaluate its activity in heavily pretreated patients with progressive myeloma.

PATIENTS AND METHODS

Patients.—All patients entered into this phase II trial had histopathologic and clinical evidence of advanced, progressive multiple myeloma which had become resistant to treatment with standard anticancer drugs, including alkylating agents, vincristine, and prednisone. All patients had measurable disease, either on the basis of a monoclonal serum paraprotein spike observed on electrophoresis and/or Bence-Jones proteinuria quantitated by electrophoresis of urine.

Treatment plan.—Mitoxantrone was administered at a dose of 12 mg/m² iv as a bolus over 15–30 minutes once every 3 weeks. Therapy was continued until evidence of progression of disease or severe or life-threatening leukopenia or thrombocytopenia (ie, wbc count < 2000 cells/mm³ or platelet count $< 50{,}000$ cells/mm³) in the absence of objective response. In patients who had a wbc count < 4000/mm³ or a platelet count $< 100{,}000$/mm³ prior to the initiation of therapy, the starting mitoxantrone dose was 9 mg/m².

Response criteria.—Myeloma cell mass determinations were calculated using the staging methods of Durie et al (1,8,9). Complete response was defined as a reduction in myeloma cell mass from a baseline of $> 75\%$ for > 1 month. Partial response was defined as a $> 50\%$ decrease in cell mass for > 1 month. Objective clinical improvement was defined as a $< 50\%$ but $\geq 25\%$ reduction in myeloma cell mass for > 1 month.

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No response was defined as a < 25% reduction in cell mass in patients receiving at least two courses of mitoxantrone treatment. Finally, increasing disease was defined as a > 25% increase in myeloma cell mass during therapy with at least two mitoxantrone treatment courses.

RESULTS

Patient characteristics.—Forty-four patients were registered in this Southwest Oncology Group phase II trial. Thirty-six of these patients were fully evaluable for response to mitoxantrone treatment. Seven patients who had had prior doxorubicin therapy were considered only partially evaluable because of early death (ie, within the first month of mitoxantrone treatment). Eighteen of the evaluable patients had had prior doxorubicin treatment and 18 had not.

Response data.—Of the 36 fully evaluable patients, only one (3%) qualified as a partial responder. This 60-year-old male had intermediate cell mass IgG kappa myeloma. He had previously received a total of five different anticancer drugs, including doxorubicin (total dose of 150 mg/m^2 over a 6-month period), melphalan, cyclophosphamide (total of 4 years of therapy), and prednisone. He had experienced a 4-year remission from disease, maintained with cyclophosphamide treatment. At the start of mitoxantrone therapy, the patient had moderately severe bone pain and a serum monoclonal IgG protein concentration of 4.8 g/100 ml. Following the fourth course of mitoxantrone, his bone pain had decreased in severity and there was a 52% reduction in serum M-component concentration and a > 50% reduction in cell mass, which lasted for 2½ months. The patient received a total of 12 courses of mitoxantrone over an 11-month period.

Four additional patients (11%) showed objective evidence of clinical improvement during mitoxantrone therapy. Two patients had had prior therapy with doxorubicin and two had not. Two patients showed approximately 25% reductions in serum M-component concentrations and marked reductions in bone pain during 4- and 10-month durations of therapy, respectively. Both had received five to six different anticancer drugs, including < 200 mg/m^2 of doxorubicin, prior to starting mitoxantrone therapy.

Two additional patients who had had no prior doxorubicin therapy showed evidence of objective clinical improvement. One patient had a 25% reduction in IgG serum M-component concentration and marked reduction in bone pain while receiving six courses of mitoxantrone over a 6-month period. The other patient had a 30% reduction in IgG serum M-component concentration while having a mild reduction in bone pain and improvement in performance status over a 7-month duration of mitoxantrone treatment. Both patients had received five different anticancer drugs prior to the initiation of mitoxantrone treatment. One of these patients had previously responded to chemotherapy, but the other patient had not responded.

Of the remaining 31 patients, 13 showed no response to therapy and 18 showed evidence of progressive disease.

Toxicity data.—Mitoxantrone was relatively well-tolerated. There were no drug-induced deaths. Myelosuppression was the dose-limiting toxicity. The median nadir wbc count was 1400/μl (range, 200–2900/μl) and the median nadir platelet count was 73,000/μl (range, 5000–214,000/μl). Seventy percent of patients experienced either severe (48%) or life-threatening (22%) leukopenia. Alopecia and nausea or vomiting were rarely observed, and there was no evidence of skin or mucous membrane toxicity.

DISCUSSION

There is a definite need for the development of new agents for the treatment of multiple myeloma. Since doxorubicin was discovered as a useful new agent in the treatment of this disease (10), only interferon appears to have proven activity as a single agent (11). The development of new drugs has been complicated by the fact that multiple-standard agents are commonly used for the induction of remission in patients with advanced disease. Mechanisms of cross-resistance between these compounds and new agents are likely to be the rule rather than the exception (12). Thus, it is a difficult task to prove useful activity for any new agent in the setting of multiple-drug resistance. Mitoxantrone has proven activity in the treatment of advanced breast cancer, acute leukemia, and advanced non-Hodgkin's lymphoma of unfavorable histology (2–7). The activity of mitoxantrone in the treatment of the latter disease suggests that it might be used effectively in the treatment of other B-cell neoplasms, including multiple myeloma.

In this phase II trial, mitoxantrone proved to have only a 3% objective partial response rate and a 14% overall objective clinical improvement rate in heavily pretreated myeloma patients. Exposure to doxorubicin did not appear to reduce the response rate to mitoxantrone therapy; however, doxorubicin pretreatment doses were relatively low in the responding patients (ie, total doses of < 200 mg/m^2). This low objective response rate to mitoxantrone was associated with a relatively low level of toxicity, essentially involving only moderate to severe leukopenia.

Based on its significant, although low level of activity in this heavily pretreated patient population, consideration should be given to future trials, incorporating mitoxantrone into new drug combinations. An example of one such combination might be the substitution of

mitoxantrone for doxorubicin in combination with the nitrosourea carmustine (13). Since mitoxantrone has been proven to be active in patients who have received doxorubicin for treatment of advanced breast cancer or non-Hodgkin's lymphoma of unfavorable history (2,3,6,7), this new anthracene compound may not be cross-resistant with the anthracycline. If this is the case, then consideration should be given to adding mitoxantrone to doxorubicin in future clinical trials in multiple myeloma.

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Drug Precipitation Within Iv Tubing: A Potential Hazard of Chemotherapy Administration[1]

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Because relatively undiluted concentrations of drugs are maintained for prolonged periods in the Y-side arm of rapidly flowing iv infusions, we visually determined compatibilities of ten commonly used cancer chemotherapy drugs and four adjunctive drugs including droperidol, metoclopramide, furosemide, and heparin. Droperidol was found to be incompatible with furosemide, methotrexate, leucovorin, heparin, and 5-FU. Furosemide was incompatible with metoclopramide, doxorubicin, vincristine, and vinblastine in addition to droperidol. Doxorubicin was incompatible with heparin. If these drugs were administered sequentially into the Y-side arm of an iv infusion, precipitation would be expected with drug inactivation and possible drug embolization to the pulmonary circulation. Flushing the Y-side arm with a compatible solution after drug administration will prevent this problem. [Cancer Treat Rep 69:1325–1326, 1985]

An easily visible, flocculent precipitate was noted in the iv tubing of chemotherapy-treated patients. Drugs administered prior to detection of the precipitate included droperidol, furosemide, and methotrexate. These agents were injected 5–60 minutes apart as a bolus into the Y-side arm of an iv infusion running at 200 ml/hour. Investigation of this phenomenon revealed that the Y-side arm served as a reservoir maintaining relatively undiluted drug concentrations for prolonged periods of time. When a second drug, incompatible with the first, was injected into the same side arm precipitation occurred (1). This precipitate, if undetected, could enter into the venous circulation, producing drug emboli. Because of this potential hazard and because bolus injection of chemotherapy into a running iv infusion is a frequent method of drug administration, we initiated a study to determine compatibilities of commonly used chemotherapy drugs and chemotherapy adjuncts.

MATERIALS AND METHODS

Ten commonly used chemotherapy drugs and four drugs often administered concomitantly with chemotherapy were tested for compatibility. Table 1 shows the drugs tested, the concentrations tested (in all cases concentrations were identical with those used clinically), and the pH of the reconstituted drug solutions (pH varies depending on the solution used for drug reconstitution). Reconstituted drugs were rapidly mixed in 0.5-ml quantities at room temperature in a 13 × 100-mm silicon-free test tube. All possible two-drug combinations were tested. Order of drug admixture was varied for all drug combinations. Precipitation was observed grossly. If no precipitate was visible, the tubes were left standing at room

TABLE 1.—Drugs tested for compatibility

Drug	Concentration	pH of reconstituted solution
Droperidol	2.5 mg/ml	3–3.8
Furosemide	10 mg/ml	8.9–9.3
Metoclopramide	5 mg/ml	2.5–5.0
Methotrexate	25 mg/ml	8.5
Leucovorin	10 mg/ml	7.8
Heparin	1000 units/ml	5.0–7.5
Cisplatin	1 mg/ml	3.5–5.5
Mitomycin	0.5 mg/ml	6–8
Cyclophosphamide	20 mg/ml	3.9–6.7
Doxorubicin	2 mg/ml	3.8–6.5
5-FU	50 mg/ml	9.0
Bleomycin	3 units/ml	4.5–6.0
Vinblastine	1 mg/ml	3.5–5.0
Vincristine	1 mg/ml	3.5–4.5

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TABLE 2.—Precipitate formation as an indicator of drug incompatibility*

	Droperidol	Furosemide	Metoclopramide	Methotrexate	Leucovorin	Heparin	Doxorubicin	5-FU	Vinblastine	Vincristine
Droperidol		+	-	+	+	+	-	+	-	-
Furosemide	+		+	-	-	-	+	-	+	+
Metoclopramide	-	+		-	-	-	-	-	-	-
Methotrexate	+	-	-		-	-	-	-	-	-
Leucovorin	+	-	-	-		-	-	-	-	-
Heparin	+	-	-	-	-		+	-	-	-
Doxorubicin	-	+	-	-	-	+		-	-	-
5-FU	+	-	-	-	-	-	-		-	-
Vinblastine	-	+	-	-	-	-	-	-		-
Vincristine	-	+	-	-	-	-	-	-	-	

*+ = precipitation; - = no precipitate.

temperature for 5 minutes and then were centrifuged for 8 minutes at 2250 × *g* in an International Clinical Centrifuge. Any sediment in the tube after centrifugation was recorded.

Infusion Sets

The iv infusion sets evaluated included the Abbott's Primary Piggyback Venoset Microdrip with Cair Clamp (No. 4968) (Abbott Hospitals, Inc, Chicago, IL) and the Travenol Continu-Flo solution administration set (No. 2C0251S) (Travenol Laboratories, Inc, Deerfield, IL). Both infusion sets have an upper and lower Y-side arm. Drugs were injected rapidly into either side arm while the iv infusion was running at 200 ml/hour. Twenty minutes later a second drug was injected into the same Y-side arm.

RESULTS

Drug compatibilities are listed in table 2. As demonstrated in this table, precipitation occurred when droperidol was mixed with furosemide, methotrexate, leucovorin, heparin, and 5-FU. Furosemide was incompatible with metoclopramide, doxorubicin, vinblastine, and vincristine in addition to droperidol. Doxorubicin was incompatible with heparin. In all cases precipitation was observed grossly immediately after the drugs were mixed. Cisplatin, mitomycin, cyclophosphamide, and bleomycin were compatible with all drugs studied.

DISCUSSION

This study demonstrates that several cytotoxic and adjunctive chemotherapy drugs precipitate when mixed together. The importance of this finding is related to our observation that the Y-side arm of iv tubing, despite flow rates up to 200 ml/hour, serves as a reservoir to maintain relatively undiluted concentrations of injected drugs for prolonged periods of time. We have noted that shortness of breath developed during chemotherapy in several patients. Whereas previously we had no explanation for this occurrence, we now believe that it might be related to undetected drug precipitates reaching the pulmonary circulation. A further problem with drug precipitation is that suboptimal drug doses may be administered to patients. This is especially true for drugs delivered in small volumes of fluid including vincristine or leucovorin. It should also be emphasized that only visually incompatible drugs were identified in this study. Microscopic precipitation and/or drug inactivation without precipitation was not evaluated. Thus, caution must be exercised in administering any drugs into the Y-side arm of iv tubing.

The drug incompatibilities that we identified might have been predicted, in many cases, from review of drug formulation (2). A major contributory factor appears to be pH-related solubility, since many of the visually observed incompatibilities occurred in solutions of widely varying pH. Order of drug admixture did not affect solubility. Other possible factors causing drug incompatibility such as concentration effects, buffering capacity of individual solutions, and temperature effects were not investigated.

Awareness that the Y-side arm of iv tubing serves as a reservoir for injected drug allows for development of techniques to prevent drug precipitation. We have found that flushing of the Y-side arm with a compatible solution after drug administration prevents precipitation. It is of interest that neither of the two infusion sets that we evaluated had any specific warning that drug retention in the Y-side arm was likely nor any directions for safe drug administration through these side arms.

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Aclarubicin Given as Continuous Infusion in Non-Small Cell Bronchogenic Carcinoma[1,2]

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Aclarubicin (ACM), a newer anthracycline antibiotic (1) with antitumor activity in murine tumors (2), is potentially clinically important because it may cause less alopecia and cardiotoxicity than doxorubicin (ADR) (3). We evaluated a 24-hour continuous iv infusion of ACM in view of possible improved therapeutic index and reduced toxicity of prolonged infusion of its analog ADR (4).

PATIENTS AND METHODS

We evaluated 24 patients with advanced non-small cell bronchogenic carcinoma (table 1). All patients had stage III disease; six had received prior ADR. ACM, obtained from the Investigational Drug Branch, National Cancer Institute (Bethesda, MD), was administered at a dose of 120 mg/m^2 as a continuous iv infusion of 24 hours through a central venous line. Treatment was repeated at 3-4-week intervals, with a median of two courses (range, one to four). Median cumulative ACM was 270 mg/m^2 (range, 120-480). Physical examination and routine tests such as hematologic and biochemical parameters and roentgenographs were performed before treatment and during each course. Cardiac function was monitored in selected patients by Holter monitor, echocardiogram, and serial ECGs. Standard response criteria were used.

RESULTS

There were no responses. All patients had disease progression within 13 weeks. Median survival was 16 weeks (range, 3-42).

Febrile episodes were seen in four patients (17%) and documented infection was seen in one (4%). One patient had gastrointestinal bleeding. Although supraventricular tachycardia, ischemic changes, and S-T depression occurred in 25% of patients, there were no clinical manifestations of cardiac dysfunction. Holter monitoring disclosed five episodes of asymptomatic arrhythmias (premature ventricular and auricular contractions and a transient short run of atrial fibrillation). Pre- and post-treatment ejection fractions measured by echocardiogram were normal. Other toxic reactions are summarized in table 2.

DISCUSSION

Cross-resistance to ADR and cumulative long-term cardiotoxicity could not be evaluated because of the small number of ADR-treated patients and of ACM courses.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total evaluated	24
Median age in yrs (range): 56 (43-73)	
Sex	
Male	16
Female	8
Tumor types	
Adenocarcinoma	13
Squamous cell carcinoma	9
Poorly differentiated carcinoma	2
Prior treatment	21
Chemotherapy	9
Radiotherapy	6
Chemotherapy + radiotherapy	6
Median performance status (range): 1 (1-4)	
Extensive/limited disease	23/1

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TABLE 2.—Toxic effects

Toxic effect	% of courses
Hematologic	
Neutrophils < 1000/mm^3	40
Platelets < 100,000/mm^3	28
Nausea/vomiting	56
Diarrhea	15
Alopecia	15
Weakness	13
Mucositis	9
Confusion	4
Anorexia	2
Facial flushing	2
Increasing liver function tests	2

The short survival indicates a poor prognostic group. ACM in this schedule was not active in refractory advanced non-small cell bronchogenic carcinoma.

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Mitoxantrone in Adenocarcinoma of the Endometrium: A Southwest Oncology Group Study[1,2]

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Few well-controlled clinical studies, utilizing single-agent chemotherapy, have been reported in patients with adenocarcinoma of the endometrium (1,2). Present studies are required to identify new chemotherapeutic agents of untested chemical configuration and non-cross-resistance with commonly used drugs. Mitoxantrone, a synthetic aminoanthraquinone whose activity appears to be mediated by intercalation into the DNA double helix, was chosen by the Southwest Oncology Group for a phase II clinical trial in patients with adenocarcinoma of the endometrium because of its significant activity against animal tumors (2), in vitro antitumor activity against human tumor colony-forming units (3,4), and its well-tolerated toxicity observed in phase I trials (5).

PATIENTS AND METHODS

Patients were considered eligible for study when histological and measurable evidence of advanced or recurrent adenocarcinoma of the endometrium, hematologic recovery following the nadir of prior cytotoxic chemotherapy, life expectancy ≥ 6 weeks, performance status ≤ 3 [Southwest Oncology Group (SWOG) standard response and toxicity criteria], and signed informed consent were present. A pretreatment leukocyte count $\leq 4000/mm^3$, platelet count $\geq 100{,}000/mm^3$, serum creatinine ≤ 1.2 mg/100 ml, and serum bilirubin ≤ 2 mg/100 ml were required. Patient characteristics are shown in table 1.

Mitoxantrone was administered iv at either an initial dose of 10 mg/m^2 (poor-risk) or 12 mg/m^2 (good-risk) in 250 ml of 5% dextrose in water over a 1-hour period every 28 days. The level of risk was determined by bone marrow reserve. Treatment was continued until increasing disease was apparent or unacceptable toxicity occurred. The dose was increased or decreased by 2 mg/m^2 when the leukocyte and/or platelet counts manifested tolerance ($\geq 3000/$ or $\geq 100{,}000/mm^3$, respectively) or excessive toxicity ($\leq 2000/$ or $\leq 50{,}000/mm^3$, respectively).

Tumor responses were assessed using standard (SWOG) criteria for complete response, partial response, stable disease, and progressive disease.

RESULTS AND DISCUSSION

Fifteen patients were evaluable for response and toxicity manifestations. Prior to mitoxantrone, 14 patients were exposed to 36 courses of chemotherapy and 11 were exposed to both radiation therapy and chemotherapy. Mitoxantrone was administered as the primary agent in one patient (7%), as second-line chemotherapy in six patients (40%), and as third- or greater-line chemotherapy in eight patients (53%). Thirteen of the 36 courses (36%) included progesterone and nonsteroidal antiestrogen drug therapy. Nine patients (60%) were previously exposed to doxorubicin.

Among 15 patients evaluable for response, eight were considered "poor risk" (10 mg/m^2) and seven were considered "good risk" (12 mg/m^2). Fifty-six courses (range, one to 18) were administered, with a median of two courses per patient. In four patients toxicity caused a reduction in dose, while in three patients tolerance and lack of myelosuppression led to an escalation of dose. Evidence of recurrent measurable disease was observed in the lungs (seven patients), pelvis (six), lymph nodes (three), abdomen and pelvis (one), and liver (one). There were no complete or partial responders. Four patients (27%)

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TABLE 1.—Patient characteristics*

Characteristic	
Eligible	15
Age (yrs)	
Median	69
Range	51-82
Measurable disease	
Pelvis	3
Pelvis + distant metastases	4
Distant metastases	8
Prior treatment	
Surgery	15
Radiation therapy	12
Chemotherapy	14
Prior chemotherapy	
Total No. of courses	36
No. of courses/patient†	2
Range	1-7
Mitoxantrone	
Total No. of courses	56
No. of courses/patient†	2
Range	1-18
Survival	
Dead of disease	14
Median duration of survival (wks)‡	17
Range (wks)	5-34

*Unless otherwise specified, values = No. of patients.
†Median value.
‡Excludes early deaths (≤ 4 wks).

maintained stable disease and 11 (73%) manifested progressive disease during therapy. Fourteen patients are dead of disease (one patient was lost to follow-up); the median duration of survival was 17 weeks (range, 5-34 weeks). No deaths were considered drug-related.

The major toxic effect was leukopenia (≤ 4000 cells/mm^3) in 11 of 15 patients (73%). The median wbc count nadir (2350/mm^3) occurred 14 days after the first day of therapy. Granulocytopenia (≤ 1500 cells/mm^3) was observed in three patients (20%) and thrombocytopenia (≤ 100,000 cells/mm^3) was observed in four (26.7%). Anemia (Hgb ≤ 10 g/100 ml) occurred less frequently (three of 15 patients or 20%), but it could not be determined whether this was tumor-related or due to drug toxicity. Nonhematologic toxicity included mild to moderate nausea and vomiting in four patients (26.7%). Cardiac toxicity was not observed.

Although mitoxantrone was associated with significant myelosuppression, it was reasonably well-tolerated by this group of heavily pretreated patients. The overall response observed in this small number of patients indicates that mitoxantrone is inactive in the treatment of advanced or recurrent adenocarcinoma of the endometrium.

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Phase II Trial of Dianhydrogalactitol in the Treatment of Children With Refractory Childhood Malignancies: A Report From the Children's Cancer Study Group[1,2]

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Investigators in the Childrens Cancer Study Group (CCSG) evaluated dianhydrogalactitol (DAG) in the treatment of children with advanced childhood malignancy who were resistant to conventional chemotherapy.

MATERIALS AND METHODS

Patients with leukemia received 50 mg/m^2/day of DAG for 5 successive days, repeated at 14-day intervals. Patients with solid tumors received 50 mg/m^2 twice a week for 4 weeks, then were maintained on 50 mg/m^2 twice weekly for 2 successive weeks every 6 weeks. Response and toxicity were reported according to CCSG criteria.

RESULTS

A total of 117 children were entered on the study. Twenty-two children received less than one course of therapy (five were early deaths, 12 refused to continue therapy, and five were errors in protocol interpretation) (table 1).

Three children with leukemia had life-threatening toxicity in the form of a serious infection associated with an absolute granulocyte count of < 500/mm^3, and three children had severe toxicity on the basis of hemorrhage associated with thrombocytopenia. In the twice-weekly schedule, one child died with gram-negative septicemia and severe leukopenia, and one child developed thrombocytopenia and died following a cerebral bleed 26 days after initiation of therapy. There was occasional, but tolerable, nausea and vomiting.

Two children with acute nonlymphocytic leukemia had a temporary (< 6 weeks) marrow reduction of blasts from > 50% to 28% and 18%, respectively. One child with medulloblastoma had a decrease in tumor size documented by computerized axial tomography on Day 74, following 12 doses of DAG. The child did not receive con-

TABLE 1.—Patient characteristics

Diagnosis	No. of patients: Evaluable/ entered	No. of patients: Partial response
Acute lymphocytic leukemia	13/16	0
Acute nonlymphocytic leukemia	13/17	2
Medulloblastoma	8/9	1
Brain stem tumors	8/10	0
Neuroblastoma	13/15	0
Wilms' tumor	7/9	0
Ewing's sarcoma	9/11	0
Other CNS tumors*	7/9	0
Sarcomas†	8/10	0
Miscellaneous tumors‡	9/11	0

*Astrocytoma (4 patients), ependymoma (3), pineal tumor (1), and retinoblastoma (1).

†Rhabdomyosarcoma (2 patients), synovial sarcoma (1), and unclassified (2).

‡Osteogenic sarcoma (2 patients), hepatoblastoma (3), teratoma (2), and lymphoma (2).

TABLE 2.—Hematologic toxicity*

Toxic effect	Schedule: Daily × 5	Schedule: Twice weekly†
ANC +/or platelet count (× 10^3)		
> 1.0 +/or > 50	1	24
0.5-0.9 +/or 25-50	0	19
< 0.5 +/or < 25	25	13
Severe infection or hemorrhage	6	2

*Values = No. of patients; sufficient data were available on 90 children for complete evaluation of hematologic toxicity.

†Two otherwise evaluable patients with neuroblastoma had bone marrow involvement with disease, and were unevaluable.

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[2]Supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Contributing Childrens Cancer Study Group investigators, institutions, and grant numbers are given in the Appendix.

†Deceased.

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comitant steroids. The patient was removed from study on Day 93 because of severe hematologic toxocity.

DISCUSSION

The dosage of DAG adopted in this study was the same or slightly higher than that reported by other investigators (1–3). Thirty-one children with leukemia and 15 children with solid tumors developed myelosuppression (table 2), which suggests that the maximum tolerable doses were used in this trial. Most patients receiving the drug were resistant to cyclophosphamide, with which DAG is known to share resistance (4). Despite one partial response in a patient with a medulloblastoma, the agent has minimal activity in children with advanced solid tumors as suggested by Wienblatt et al (3). DAG appears to be inactive against advanced acute leukemia and advanced neuroblastoma in children.

APPENDIX

Principal Investigators of the Childrens Cancer Study Group

Institution	*Investigator*	*Grant No.*
Group Operations Office, University of Southern California Comprehensive Cancer Center, Los Angeles	Denman Hammond John Weiner Harland Sather Richard Sposto Mark Krailo Jonathan Buckley	CA-13539
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Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH	Peter Coccia Samuel Gross	CA-20320
Children's Hospital National Medical Center, George Washington University, Washington, DC	Sanford Leikin	CA-03888
Children's Memorial Hospital, Northwestern University, Chicago, IL	Helen Maurer George Honig	CA-07431
Children's Hospital of Los Angeles, University of Southern California	Jorge Ortega Gussie Higgins	CA-02649
Children's Hospital of Columbus, Ohio State University	Frederick Ruymann	CA-03750
Babies Hospital, Columbia University, New York, NY	Sergio Piomelli James Wolff	CA-03526
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Principal Investigators of the Childrens Cancer Study Group (cont'd)

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University of Texas Health Sciences Center, San Antonio	Paul Zeltzer Thomas Williams	CA-36004
Children's Hospital of Philadelphia, University of Pennsylvania	Audrey Evans	CA-11796
Memorial Sloan-Kettering Cancer Center—Cornell University, New York, NY	Denis R. Miller	CA-23742
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University of Utah Medical Center, Salt Lake City	Richard O'Brien Eugene Lahey	CA-10198
Strong Memorial Hospital, University of Rochester, NY	Harvey Cohen Martin Klemperer	CA-11174
University of British Columbia, Vancouver, Canada	Mavis Teasdale	Vancouver Foundation grant CA-29013
Children's Hospital Medical Center, University of Cincinnati, OH	Beatrice Lampkin	CA-26126
Harbor University of California at Los Angeles and Miller Children's Medical Center, University of California, Los Angeles, Torrance, and Long Beach	Jerry Finklestein	CA-14560
University of Iowa Hospitals and Clinic, Iowa City	Raymond Tannous	CA-29314
Mayo Clinic, Rochester, MN	Gerald Gilchrist	CA-28882
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Phase II Trial of Etoposide, Vincristine, and High-Dose Cisplatin in Advanced Non-Small Cell Lung Cancer[1]

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Cisplatin, given with etoposide or vinca alkaloids, has demonstrated synergistic therapeutic activity in both animal models and clinical trials (1-3).

Twenty-two patients with advanced non-small cell lung cancer (NSCLC), previously unexposed to chemotherapy, were treated with a combination of vincristine (1.4 mg/m^2 iv) on Day 1, cisplatin (40 mg/m^2 iv) on Days 1-3, and etoposide (100 mg/m^2 iv) on Days 1-3 (or 80 mg/m^2 iv on Days 1-3 for patients previously treated with radiation). Because six of the first nine patients entered in this trial (Group 1) experienced granulocytopenia of < 1000 cells/mm^3, the initial dose of etoposide was decreased to 80 mg/m^2 (or 60 mg/m^2) for the remaining 13 patients (Group 2). The second treatment cycle was given 4 weeks later; subsequent cycles were repeated every 6 weeks. Etoposide was decreased by 50% if severe hematologic toxicity was observed.

Histologic proof of stage IV NSCLC, bidimensionally measurable disease, and normal hematologic, renal, and hepatic functions were required for study entry. Patient characteristics are reported in table 1. Diagnoses included squamous cell carcinoma (ten patients), adenocarcinoma (three), large cell carcinoma (two), and undifferentiated NSCLC (two). Six patients had had previous radiation therapy.

Six responses (duration calculated from the first day of treatment) were achieved, two in Group 1 and four in Group 2. One complete response (disappearance of all clinical evidence of disease) of 10.6 months' duration and five partial responses (≥ 50% decrease in tumor area) of 3.9 months' median duration were observed (response rate, 27%). Median duration of stable disease in 13 patients was 4.0 months (range, 2-12 months). Three patients had disease progression within the first two courses of therapy.

Nausea and vomiting were universal but controllable by antiemetics. Two patients in Group 2 experienced transient mild alterations of kidney function tests. The dose-limiting toxicity was myelosuppression, despite the dose reduction of etoposide (table 2). Substantial neurotoxicity was observed with the higher dose of etoposide. In Group 1, six of nine patients had neurotoxic effects, and all experienced either paresthesias, tinnitus, or dizziness; in addition, two patients had abolition of deep tendon reflexes and one patient had an episode of paralytic ileus. In contrast, only one of 13 patients experienced paresthesias and decrease in deep tendon reflexes in Group 2. No treatment-related deaths were reported.

DISCUSSION

In this series, an increased dose of etoposide given in combination with vincristine and high-dose cisplatin was associated with a higher incidence of neurotoxic effects. Unlike the results reported by Gralla et al (3), the use of

TABLE 1.—Patient characteristics

Characteristics	No. of patients
Median age in yrs (range): 59 (31-71)	
Median performance status (range): 90 (70-100)	
Males/females	11/11
Organ involvement	
Intrathoracic site*	22
Liver	3
Bone	3
Soft tissue†	11

*Lung, pleura, bronchus, mediastinum, hilum, and malignant pericardial effusion (1 patient).

†Extrathoracic adenopathy, skin, chest wall, and retroperitoneum.

[1]Received Nov 2, 1984; revised Apr 1, 1985; accepted Apr 5, 1985.

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TABLE 2.—Drug toxicity

Toxicity	No. of patients	
	Group 1*	Group 2†
Wbc count nadir (× 10^3 cells/mm^3)		
⩾ 4.5	2	—
3 to < 4.5	—	4
2 to < 3	3	5
1 to < 2	2	3
⩾ 1	1	1
No information	1	—
Granulocyte count nadir (× 10^3 cells/mm^3)		
⩾ 1.9	1	—
1.5 to < 1.9	1	1
1.0 to < 1.5	—	1
0.5 to < 1.0	2	5
< 0.5	4	6
No information	1	—
Platelet count nadir (× 10^3 cells/mm^3)		
⩾ 130	4	8
90 to < 130	1	1
50 to < 90	3	2
25 to < 50	—	—
No information	1	—

* 100 (80) mg/m^2 iv of etoposide on Days 1–3.
† 80 (60) mg/m^2 iv of etoposide on Days 1–3.

high-dose cisplatin failed to prolong the duration of response. This trial supports the conclusion of the European Organization for Research on Treatment of Cancer (4) that this type of triple combination chemotherapy is not recommended for the treatment of NSCLC.

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Phase II Trial of 4′-Deoxydoxorubicin in Advanced Non-Small Cell Lung Cancer[1]

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4′-Deoxydoxorubicin (4′-deoxyDX) is a derivative of doxorubicin which lacks the hydroxylic group in the 4′ position of the aminosugar (1). It has shown significant activity against a variety of experimental tumor systems (2). In animal models, 4′-deoxyDX has been shown to be appreciably less cardiotoxic than doxorubicin (3). Phase I studies showed myelosuppression to be dose-limiting, and iv administration of 30 mg/m^2 on an every-3-week schedule was proposed for phase II trials (4,5). We report the results of a phase II study with 4′-deoxyDX in patients with advanced non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

Thirty-eight patients with histologically or cytologically proven NSCLC entered the trial. Patient characteristics are summarized in table 1. Criteria for entry in the study included measurable or evaluable disease, performance status of 0–3 [World Health Organization (WHO)], no prior anthracycline therapy, wbc count $\geq$ 3500/mm^3, platelet count $\geq$ 100,000/mm^3, bilirubin $\leq$ 1.5 mg/dl, and serum creatinine $\leq$ 1.5 mg/dl. Nineteen (50%) patients had received no prior chemotherapy or radiation therapy. (4′-DeoxyDX was supplied by Farmitalia Carlo Erba, Milan, Italy.)

The drug was administered iv at a starting dose of 30 mg/m^2 every 3 weeks. Cbc and platelet counts were monitored on a weekly basis, and subsequent doses were escalated by 20% (to 36 mg/m^2) if no myelosuppression occurred. Standard response criteria were employed. Two courses of 4′-deoxyDx had to be administered for the trial to be considered adequate.

RESULTS

Thirty-three patients received an adequate trial. Hematologic toxicity was the most commonly encountered toxic effect (table 1). A total of 149 doses was administered (median, three; range, one to 19). No cumulative myelosuppression was detected. Gastrointestinal toxicity and alopecia were not troublesome (table 1). No

TABLE 1.—Patient characteristics

Characteristics	No. of patients
Entered	38
Males/females	32/6
Median age in yrs (range): 66 (43–75)	
WHO performance status	
0–1	29
2–3	9
Prior treatment	
Chemotherapy	7
Radiotherapy	12
None	19
Stage of disease	
Extensive	33
Limited	5
Histologic type	
Squamous cell carcinoma	19
Adenocarcinoma	8
Large cell carcinoma	8
Undifferentiated carcinoma	3
Hematologic toxicity	
Median wbc count nadir (range): 2200/mm^3 (550–4300)	
Median platelet count nadir (range): 160,000/mm^3 (57,000–320,000)	
Nausea and vomiting	
Grade 1	9
Grade 2	4
Grade 3	2
Alopecia	
Grade 1	5
Grade 2	1
Grade 3	1

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objective responses were observed (95% confidence limits, 0%–10.6%). There were 21 patients with no progression (median, 90 days; range, 45–408).

DISCUSSION

Most patients had good performance status and 50% of them were previously untreated. Treatment was well tolerated. Although myelosuppressive doses were used, no responses occurred. We conclude that 4′-deoxyDX at this dose and schedule does not appear to have any substantial activity in advanced NSCLC.

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Clinical Predictivity of Transplantable Tumor Systems in the Selection of New Drugs for Solid Tumors: Reply to a Commentary

Martin et al (1) have recently published a commentary on our analysis (2) of the strategy introduced by the National Cancer Institute (NCI) in 1975 to identify potentially clinically effective drugs using transplantable tumor systems in mice. The overall correlation of results in the animal systems and in clinical studies as described in our paper is not high, and Martin et al attribute this to the use of different endpoints, namely, tumor regression in clinical studies in contrast to inhibition of tumor growth in animal models. We agree that the choice of endpoint for a screening model may influence its clinical predictivity. However, the statements by Martin et al that our conclusions may be "entirely incorrect" and the "significance" of our comparisons "cannot be considered valid" indicate basic misunderstandings on their part, and much of their commentary is irrelevant to the evaluation of the NCI screening strategy.

The first point that we wish to make is that we undertook an evaluation of the then-current NCI strategy, which was based on a prescreen and a panel of eight screens. For these eight screens, we had available only whether the test was positive or negative based on the "confirmatory level" criteria (Decision Network Phase 2) then in use. Given the standard definitions for positivity in each screen, the comments of Martin et al are irrelevant to the correctness and validity of our conclusions. Where to set the cutpoint for a particular test is a separate issue, which we addressed for the prescreen but which was not the subject of our paper with regard to the eight screens of the panel. Martin et al show only one table with test results, which makes the completely obvious point that setting a cutpoint at a lower level will increase the number of results declared positive. Considerations of where to set cutpoints are best done not by discussing correlations, but by investigating quantities such as the positive predictive value, negative predictive value, specificity, sensitivity, and yield of a screen. Stated another way, two kinds of errors (false positives and false negatives) must be considered and their relative importance depends on the goals of the procedure. Our suggestions for a multistage strategy included such considerations for making appropriate joint use of screens with either high sensitivities or specificities (relative to the other screens and based on the established cutpoints).

In general, the strategies we discussed were based on the idea that an important part of current efforts should be to increase the number of potentially clinically effective agents available. In such a setting, it would be more important not to miss any truly effective drugs, even though a larger number of false positives may temporarily be advanced for further testing. A different viewpoint, which placed a premium on having a high probability of success before advancing a drug for clinical testing, would place greater emphasis on high specificity. In our proposed strategy, this would involve increased attention to the optional third stage consisting of screens with relatively high specificity.

The definition of criteria of response involves a number of other considerations. Selecting an endpoint for a particular screen is a separate issue from defining a cutpoint for positivity based on that endpoint. Some of the screens in the NCI panel that we analyzed were based on survival time; others were based on tumor growth inhibition expressed as weight of tumor. In addition, the properties of a screening strategy depend on how the results of various screens are used together; this was an important focus of our paper.

Finally, the biological characteristics of the various screens must be considered. Martin et al mention the importance of tumor burden in determining the response to chemotherapy. In our paper we listed a number of concepts that play a role in the design of screening systems, including not only tumor burden but also origin of the tumor and the specifics of transplantation or cell culture. The aim in developing new systems should be to increase both sensitivity and specificity. While using the "same endpoints" in animals and humans appears to be a sensible approach, it is not necessarily true that in practice the best screens will be those that are based on this advice of Martin et al. Data rather than arguments alone must be presented to support the claims for the superiority of any particular system. Also, as we discussed in our paper, consideration must be given to sources of bias that are often present in investigations of the clinical predictivity of screening systems.

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Hypoglycemia: Not an Important Side Effect of Mitoguazone

In June 1983, five deaths were reported in a phase II study of mitoguazone (methylglyoxal bisguanylhydrazone; MGBG) to the Investigational Drug Branch of the National Cancer Institute (NCI). Two deaths were associated with hypoglycemia preterminally. Because it was not clear in these patients whether hypoglycemia was a significant factor in their demise, or, more importantly, whether the hypoglycemia was a consequence of MGBG, monitoring of weekly or biweekly blood glucose levels was requested in patients accrued to MGBG protocols. We report here the rationale for the implication of MGBG as a possible cause of hypoglycemia and the subsequent experience with this complication over the past 18 months.

MGBG is an inhibitor of *S*-adenosylmethionine decarboxylase (1). In addition, it inhibits State 4 mitochondrial respiration, probably by preventing cation flux across the mitochondrial membrane (2). This inhibition is increased by concomitant exposure of cells to phenylethylbiguanide (phenformin), which also potentiates the antiproliferative activity of MGBG against L1210 leukemia in vitro (3). Inhibition of mitochondrial respiration may explain the early observation of an inhibitory effect of MGBG on oxidative phosphorylation in L1210 leukemia in mice (4). In addition, inhibition of mitochondrial respiration may reasonably be postulated to cause a decrease in the substrates for gluconeogenesis. The summation of these phenomena could lead to clinically evident hypoglycemia.

In the preclinical toxicology studies, lethal hypoglycemia was observed in rats, rabbits, guinea pigs, and monkeys (5). Hypoglycemia was associated with focal hepatic necrosis in rats, and in rabbits (with massive hepatic necrosis and occasionally with renal tubular damage). In monkeys and guinea pigs, hypoglycemia was described with both hepatic and renal damage.

The deaths reported in 1983 generated a high level of awareness to hypoglycemia in subsequent clinical studies. However, this complication has not been recurrent since that time. A review of NCI contract reports, cooperative group minutes, and Phase I and II Working Group minutes did not identify hypoglycemia as a side effect of MGBG. No further adverse drug reactions involving hypoglycemia have been reported for MGBG since June 1983. Furthermore, laboratory data are available on 112 of the 802 patients treated on multiple phase I, II, and III studies between June 1983 and September 1984. In most cases, blood glucose determinations were performed at weekly intervals, before the next dose of MGBG. In no patient from this sampling was the blood glucose determination < 59 mg/dl. Based upon the collective experience accumulated over the past 18 months and the results of this sampling, we conclude that hypoglycemia is not a major toxic effect of MGBG as currently used. Therefore, routine monitoring of blood glucose does not seem to be necessary during treatment with MGBG.

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Advanced Ovarian Carcinoma: Response to the Agonist D-Trp-6-LHRH

There have been several reported studies where ovarian carcinoma has responded to hormonal manipulation with antiestrogen and progesterone therapy (1,2). Here we describe a patient who responded dramatically to D-Trp-6-LHRH (Decapeptyl).

CASE REPORT

A 78-year-old woman presented in February 1981 with an inoperable bilateral ovarian tumor. Histology showed a moderately differentiated serous cystadenocarcinoma of the ovary. She was treated with cisplatin (30 mg iv) and chlorambucil (5 mg/day orally for 7 days), repeated at 4-week intervals. The patient received 12 courses of treatment. However, a second-look laparotomy in November 1982 showed a large ovarian tumor adherent to the lateral pelvic wall. The tumor was removed and was found to be of the same histology. A course of radiotherapy was given, and was completed in March 1983. In June 1983, a mass was noted in the right iliac fossa and the patient was started on treosulphan. However, she became pancytopenic and the treosulphan had to be stopped. She had several whole blood and platelet transfusions as an in-patient, and was treated with broad-spectrum antibiotics when she became pyrexial with a wbc count of 1.0×10^9/L.

The bone marrow gradually recovered, and in January 1984, a pelvic ultrasound showed a mass of $7 \times 8 \times 8$ cm^3 on the right side of the pelvis. In view of the recent severe marrow toxicity and recurrence of the tumor, the patient was started on D-Trp-6-LHRH, after giving written informed consent. This was initially given as 100 μg/day sc for 28 days. Subsequently, she was maintained on a monthly im injection of a slow-release preparation of D-Trp-6-LHRH microcapsules designed to release 100 μg/day. Two months after starting treatment, her basal levels of gonadotropins were markedly suppressed (table 1). The mass was very much smaller clinically, and a repeat ultrasound at 5 months was reported: "the previously noted right-sided pelvic mass appears to have almost totally resolved and there is now only a residual $2 \times 2 \times 1.5$-cm^3 solid area at the side of the previous mass." In conjunction with the shrinkage of the tumor, the CEA levels fell from 22 to 3 μg/L at 10 months (normal range < 10 μg/L). The patient remained in clinical remission for 12 months, when she relapsed with abdominal ascites and metastatis to the lungs. Since relapse, the treatment with D-Trp-6-LHRH has been stopped.

DISCUSSION

Luteinizing hormone (human chorionic gonadotropin) receptors have been identified in malignant ovarian tumors (3), and gonadotropins have been implicated in ovarian carcinogenesis (4).

Schally et al (5) have demonstrated that chronic administration of analogues of gonadotropin-releasing hormone results in paradoxical inhibition of pituitary gonadal function (5). Therefore, it seems timely to assess the possible benefits of D-Trp-6-LHRH as a simple treatment of advanced ovarian carcinoma which seems free of clinical, hematological, or biochemical side effects.

At present, we are carrying out a larger prospective study to assess the clinical efficacy of D-Trp-6-LHRH in advanced ovarian carcinoma. We hope that this may acquire a useful and nontoxic role in the treatment of advanced ovarian carcinoma.

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TABLE 1.—Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels (units/L)

	Pretreatment (mos)	Posttreatment (mos)				
	0	2	4	6	8	10
FSH	33.5	2.0	3.1	3.3	3.9	3.2
LH	25.2	3.0	2.4	2.6	2.2	2.0

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Liver Enzyme Abnormalities After Poly ICLC Infusions

Poly ICLC has been used investigationally for the induction of endogenous interferon production in patients with a wide spectrum of diseases. The typical febrile response and other symptoms resembling an acute influenza attack are reversible; patients normally recover without further sequelae. Here we report a case in which high liver enzyme values resulted after each of 13 poly ICLC infusions.

A 35-year-old male was admitted with a diagnosis of multiple sclerosis and was enrolled in a protocol to receive the investigational interferon inducer polyinosinic, polycytidylic acid stabilized with poly-L-lysine (poly ICLC). The baseline laboratory values for this patient were all within normal limits. The patient occasionally consumed alcohol, and was medicated only with oxybutynin (5 mg three times a day). The usual influenza-type syndrome associated with poly ICLC was noted after each of 13 infusions, and the plasma cortisol and plasma interferon levels increased, as was typical in other patients admitted to the study.

The liver enzymes, however, were also transiently elevated over periods varying from 1 week to 2 months. The SGPT was elevated after each infusion, the SGOT was elevated after 92% of the infusions, LDH was elevated after 46% of the infusions, and alkaline phosphatase was elevated after 54% of the infusions. The average maximal percent increase over average baseline values for all infusions was 815% for SGOT, 1949% for SGPT, 18% for LDH, and 9% for alkaline phosphatase. This represented a substantial problem in our patient, since the drug had no adverse clinical effects except for the immediate influenza-like syndrome following each dose. Since the patient was well enough to go "on pass," the duration of the elevation was difficult to ascertain, but generally lasted for about a week after each dose (except once when the elevation persisted for 2 months). Our patient had no clinical symptoms of hepatic disease over the next 8 months, despite similar enzyme elevations associated with each poly ICLC infusion.

We feel that the elevations were great enough and sustained enough to warn others of the possible adverse reactions. A previous report by Nakamura et al (1) revealed modest elevations in the SGOT and SGPT in one patient, which persisted for a few days. The actual dose that the patient received approximated the dose that our patient received. The report by Sakakibara et al (2) adds a bit of irony to the matter, because they showed that poly IC protected rat livers from galactosamine-induced injury. To our knowledge, there are no other reports of hepatic abnormalities from poly ICLC.

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Skeletal Muscle Biopsies in Patients Treated With Doxorubicin

Doxorubicin is an effective antineoplastic drug. Unfortunately, its use is limited by cardiotoxicity, which includes myocardial damage histologically consisting of myofibrillar loss, distension of sarcoplasmic reticulum, loss of organelles, and mitochondrial and nuclear degeneration (1).

Noninvasive tests, such as ECG and ejection fraction examinations, have not been able to predict this damage, while myocardial biopsies have shown a useful correlation between morphology and the total cumulative dose of doxorubicin (2). The myocardial damage is dose-related, and at doses > 500 mg/m^2, virtually all patients show at least a mild degree of cardiomyocyte damage (2).

The effect of doxorubicin on normal tissues has been studied in rats, where skeletal muscle damage similar to the myocardial findings has been observed after iv administration (3,4), and identical concentration of the drug was observed in skeletal and heart muscle after ip

TABLE 1.—Patient characteristics*

Patient No.	Age (yrs)	Sex	Previous heart disease	Pretreatment values (%)							Posttreatment values (%)							Clinical sign of heart failure following doxorubicin
				ECG		LVEF		RVEF		Angiocardiography	ECG		LVEF		RVEF		Angiocardiography	
				R	E	R	E	R	E		R	E	R	E	R	E		
1	65	F	No	N	MP	73	64	34	61	N	N	N	51	62	—	—	Hypokinesia and akinesia	No
2	65	F	No	N	MP	66	68	43	—	Hypokinesia	N	N	39	59	48	55	Hypokinesia	No
3	50	F	No	N	MP	60	43	50	72	Hypokinesia	SP	SP	21	29	21	32	Hypokinesia	Died from cardiomyopathy
4	41	F	No	N	—	—	—	—	—	—	N	N	55	71	43	47	N	No
5	53	F	No	N	—	—	—	—	—	—	N	N	59	68	—	—	N	No
6†	47	F	No	N	—	—	—	—	—	—	—	—	—	—	—	—	—	No

*LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; R = rest; E = exercise; N = normal; MP = moderately pathological; SP = severely pathological; and — = no values obtained.

†Patient 6 refused all tests except for pretreatment ECG (rest).

administration (5).

This study investigated whether skeletal muscle biopsies could predict cardiotoxicity in patients treated with doxorubicin.

MATERIALS AND METHODS

Six patients with disseminated solid tumors were treated with doxorubicin at a maximum dose of 550 mg/m^2. Muscle biopsy was performed in local anesthesia from the lateral vastus muscle within 5 weeks after cessation of doxorubicin therapy.

Light microscopy.—In sections stained with hematoxylin-eosin, periodic acid-Schiff, and Van Gieson's stain muscle cell diameter, cross-striation, sarcoplasmic density, distribution of glycogen, nuclear morphology, interstitial edema, and fibrosis were investigated.

Transmission electron microscopy.—The morphology of myofibrils, mitrochondria, nuclei, and nucleoli was studied, and there was a search for lipid droplets.

Cardiac status was evaluated using clinical examinations, ECG, and radionuclide angiocardiography, with determination of ejection fraction of right and left ventricle during rest and exercise. Three patients had all the measurements done before, during, and after doxorubicin therapy. Two patients had angiocardiography done only after cessation of doxorubicin, and one patient refused this evaluation.

RESULTS

In the muscle biopsies, no changes from the normal were found in the observed features. Clinical signs of cardiomyopathy were observed in one patient who died of congestive heart failure 2 months after cessation of treatment. Two other patients showed a significant decrease in cardiac function during therapy, while two patients had normal cardiac evaluation. Patient characteristics are shown in detail in table 1.

DISCUSSION

In animal studies, histological changes have been observed in the myocardium and skeletal muscle after high doses of doxorubicin therapy, and Lefrak et al (6) have found identical histological changes in these tissues at autopsy in a patient with doxorubicin cardiomyopathy. Doroshow et al (7) found parallel changes in the myocardium and diaphragm 4 days after therapeutic doses of doxorubicin were given ip to mice. However, changes in the gastrocnemius muscle were limited to a slight increase in the number of lipid droplets.

The present pilot study failed to demonstrate changes in the skeletal muscles, although three of the six patients had impaired heart function after cessation of doxorubicin therapy. The explanation may be that myocyte damage in the vastus muscle either does not occur or is slight and reversed shortly after cessation of treatment. We must therefore conclude that skeletal muscle biopsies in this small group of patients had no value in predicting doxorubicin cardiomyopathy.

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Association for Brain Tumor Research Opens Applications for 1986 Postdoctoral Fellowships

The Association for Brain Tumor Research (AFBTR) fellowships offer an award of $18,000 per annum plus a $2000 annual travel allowance for a period of 2 years, with a third-year renewable option. Each year's travel must include one presentation to the AFBTR Board of Directors in Chicago.

Preference will be given to MDs who are US citizens or permanent residents of the US, seeking research training that will enable them to pursue careers as clinical investigators. All applications will be reviewed by the Association's Medical Advisory Council and awards will be made based on their recommendations. Criteria for selection will include the quality of the individual applicant; the quality of the program to which s/he is applying; and the research s/he is undertaking.

Applications must be submitted by the sponsoring program director, and the deadline for completed applications, including letters of recommendation, is January 10, 1986. Awards will be announced by April 1, 1986, for fellowships to begin July 1, 1986.

Presently, the Association is sponsoring Fellowships at Duke University, Durham, NC; Memorial Sloan-Kettering Cancer Center, NY; Massachusetts General Hospital, Boston; University of North Carolina at Chapel Hill; and Johns Hopkins University, Baltimore, MD.

Application forms may be obtained from the Association for Brain Tumor Research, Suite 200, 6232 N Pulaski Rd, Chicago, IL 60646. Completed applications should be mailed to the same address.

For further information, contact: Donald Segal, Executive Director, Association for Brain Tumor Research, Suite 200, 6232 N Pulaski Rd, Chicago, IL 60646 (telephone: 312-286-5571).

Medtech '86: International Symposium on Cancer Biology and Therapeutics

Tampa, Florida, January 20–22, 1986

The University of South Florida-College of Medicine and the City of Tampa-International Trade Fair Advisory Board and International Conference Management, Inc, are sponsoring the 1st Annual International Symposium on Cancer Biology and Therapeutics at the Curtis Hixon Convention Center, Tampa, FL. Major topics include: biochemistry of the cancer cell in selectivity of drug action; biological and clinical implications of the tumor cell; approaches to the diagnosis and treatment of cancer; clinical advances and problems in the treatment of human tumors; induction, prevention, and modulation of cancer; and immunological viral aspects of neoplasia.

The symposium qualifies for 21 Category 1 CME credits.

For further information, contact: International Conference Management, Inc, 15851 Dallas Pkwy, Suite 1155, Dallas, TX 75248 (telephone: 214-458-7011).

Progress in Gynecological Oncology

Los Angeles, California, February 12, 1986

The Hospital of the Good Samaritan is sponsoring a symposium on the progress in gynecological oncology to be held at the Moselely-Salvatorie Conference Center. This symposium will be acceptable for up to 6 hours of Category 1 Credit toward CMA and AMA certificates in Continuing Medical Education.

Fees are as follows: $85.00 for practicing MDs and $45.00 for allied health professionals, interns, residents, fellows, and retired MDs. A luncheon will be included in the fee.

For further information, contact: Dolores Gay, The Hospital of the Good Samaritan, 616 S Witmer St, Los Angeles, CA 90017 (telephone: 213-977-2352).

Clinical Hematology and Oncology: 1986

San Diego, California, February 17–19, 1986

Vacation Village Resort will be the site for this conference designed for hematologists, oncologists, internists, pediatricians, and pathologists interested in the diagnosis and management of hematological and oncological disorders. Sponsored by Scripps Clinic and Research Foundation of La Jolla, California, this conference will offer Category I credit.

For further information, contact: Bonny Mower, Department of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037 (telephone: 619-457-8556).

Arizona Cancer Center 5th Winter Symposium on Advances in Clinical Oncology

Snowbird, Utah, March 8–15, 1986

For further information, contact: Mary Humphrey, conference coordinator, Arizona Cancer Center, Tucson, AZ 86724 (telephone: 602-626-6044).

Postgraduate Course on Functional and Stereotactic Neurosurgery

Garmisch-Partenkirchen, West Germany, March 9–16, 1986

The University of California at San Francisco is sponsoring a postgraduate course on functional and stereotactic neurosurgery to be held at the Holiday Inn in Garmisch-Partenkirchen, West Germany. This symposium is designed to encourage the exchange of medical information on selected topics in functional and stereotactic neurosurgery between physicians from Europe and the United States. Topics to be discussed include: spinal cord stimulation for peripheral vascular diseases; implanted drug delivery system for the control of pain and spasticity; trigeminal ganglionic stimulation for the control of atypical facial pain; brain stimulation for the control of chronic pain; CT guided stereotactic tumor biopsy and demonstration of BRW system; technique and results of stereotactic brain tumor irradiation by permanent radioactive nuclide implants and intracystic therapy; technique and results of stereotactic brain tumor irradiation by removable radioactive nuclide implants; and the effects of focal irradiation on normal brain. In addition to the didactic sessions, selected papers related to the topics will be presented by participants. This course offers 20 hours of credit in Category I.

Submissions are welcome and should be sent to the Program Director.

For further information, contact: Extended Programs in Medical Education, University of California School of Medicine, Rm 569-U, San Francisco, CA 94143 (415-666-4251).

Sixth Annual Symposium on Fine Needle Aspiration

Budapest, Hungary, August 9–16, 1986

The Department of Pathology at the University of California School of Medicine in San Francisco and The Society of Hungarian Pathologists in cooperation with the Californian Society of Pathologists are sponsoring the Sixth Annual Symposium on Fine Needle Aspiration to be held at the Atrium Hyatt Hotel, Budapest, Hungary. This symposium is designed to provide a comprehensive introduction to fine needle aspiration biopsy techniques and interpretive criteria. Tuition includes lectures, extensive syllabus, kodachrome study set, FNA performance, microscopes, microscopy sessions, and case presentations. The symposium offers ACCME/AMA/CMA Category 1 credits.

For further information, contact: Extended Programs in Medical Education, Rm 569-U, University of California School of Medicine, San Francisco, CA 94143 (415-666-4251).

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